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TRUTH AND POETRY

Concerning

URIC ACID

AN EPITOME OF THE PRESENT STATE OF KNOWLEDGE OF THE SUBJECT AS PRESENTED IN THE LITERATURE

BY

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PREFACE

WHEN the following articles were begun as editorials in THE JOURNAL of the American Medical Association, I had no idea that they would be reprinted subsequently, much less that they would be republished under my name. Requests that all the articles be united, however, have been received and THE JOURNAL has decided to issue them, as collected, in the present form.

I have hesitated to attach my name to the reprint, since it is not a report of clinical and laboratory work of mine, but simply a review of the work of others. If, however, the pamphlet be successful in helping to clarify the ideas of American practitioners regarding the complex questions discussed, and, especially, if it protect physicians and, through them, the public, to a certain extent from the nostrum mongers who are misleading not only the profession but the public by their claims based on a theory that has long been recognized as fallacious, I shall be glad to have assumed the responsibility of compiler.

No one who grows can escape the pain of being forced, now and then, to sacrifice dearly cherished opinions; but if truth be followed, a satisfaction is always gained superior to that which has been lost. Emerson put it well:

Heartily know,
When half-gods go
The gods arrive.

LEWELLYS F. BARKER.

BALTIMORE, Nov. 15th, 1905.

TABLE OF CONTENTS.

PAGE.

CHAPTER I.

Introduction 1

CHAPTER II.

Discovery of Uric Acid and Early Theories Concerning It 6

CHAPTER III.

Proof of the Origin of Uric Acid from Nuclein.... 11

CHAPTER IV.

Uric Acid Arises from the Nuclein of all the Body-Cells; not Simply from Leucocytic Nuclein.. .. 16

CHAPTER V.

Demonstration That Uric Acid Arises Also from the Nucleins and Xanthin Bases of Ingested Food: Origin of the Conception of Exogenous and Endogenous Purins 22

CHAPTER VI.

Uric-Acid Formation in Man Chiefly Oxidative, but Possibly Also Synthetic..... 27

CHAPTER VII.

Destruction of Uric Acid Within the Body..... 34

CHAPTER VIII.

Localization Within the Body of the Processes of Uric-Acid Formation and Uric-Acid Destruction. 40

PAGE.

CHAPTER IX.

The Stereochemistry of Uric Acid and of Some Other Purin Bodies. The Urates and Their Solubility.. 44

CHAPTER X.

The Uric Acid and Urates of the Urine and of the Blood and Lymph 49

CHAPTER XI.

Uric Acid in Disease. Its Pathologic Physiology.. 54

CHAPTER XII.

The Excess of Uric Acid in the Blood in Gout..... 58

CHAPTER XIII.

The Excretion of Uric Acid in Gout. It Relation to the Excess in the Blood 63

CHAPTER XIV.

The Total Nitrogen and the Total Phosphoric-Acid Metabolism in Gout 71

CHAPTER XV.

Other Factors Possibly Concerned in Occasioning the Excess of Uric Acid in the Blood in Gout.... 75

CHAPTER XVI.

The Relation of Uric Acid (or Urates) to Gouty Deposits and to the Acute Gouty Paroxysms.... 80

CHAPTER XVII.

Therapeutic Measures Directed Toward Influencing Uric-Acid Formation, Destruction and Excretion. The Treatment of Gout 86

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CHAPTER I.

INTRODUCTION.

New Facts and Theories Concerning Uric Acid Only Slowly Assimilated by the Profession—Reasons Therefor—Facile Publications—Unbridled Commercialism—Purpose of the Present Review.

In the slow but steady advance which medicine is making, new facts are often established for a long time before they meet with general acceptance, and old theories have had their foundations washed out from under them years or decades before their fallacies have become generally recognized by the profession. It is easy to be too severe in criticizing the inertia of medical men in this respect, for the very conservatism which accounts for the facts mentioned has gone far to protect our guild from the too speedy welcoming of immature conceptions, on the one hand, and from the too easy rejection, on the other, of theories which, under assault by partisan or ignorant critics, prove ultimately to be sound. It is not an unwillingness to accept new truth nor a desire stubbornly to retain error which is characteristic of our profession. On the contrary, it is rather the fear of being duped concerning the new or of being cheated of old and well-tried good which animates it and determines its action or inaction.

Now that the media of communication among physicians have been so marvelously multiplied, it may be urged that the excuse for a continuance in ignorance regarding medical facts and theories is not what it formerly was. Medical journals are,

it is true, more widely read than ever before by the profession; the nations, through the activity of collective reviews and international periodicals, have been brought closer together than at any previous time; were the increased information brought to medical readers always reliable, the profession's knowledge ought to be advanced by leaps and bounds. Unfortunately, at a time when everybody writes, the views which are expressed in the various medical journals are so contradictory that the mind without a special scientific training often becomes confused, knows not what to believe, and naturally settles down on the convictions which suit its own inclination best or on statements which have been gained from some authority for which it has a particular predilection. The preliminary training which the average medical man has obtained hitherto in subjects like chemistry, physics and biology has been totally inadequate, when discussions involving disputes in these domains are brought to his attention, to permit him to form sound judgments concerning them. A further difficulty for the medical man in practice lies in the inequality of the articles which are admitted to the pages of even those medical journals which he has been taught to regard as the best. So disparate are the views expressed in different articles in the same number of a given journal that the average medical mind often turns from the reading of them with a feeling of uncertainty, if not of disgust.

It is one of the objects of THE JOURNAL in its editorial pages to present, from time to time, as accurately as it can, synopses of the real advances which take place in medical research. It is and has been its endeavor to promulgate as firm convic-

tions in these columns only those views which receive the support of what it regards as the soundest medical judgment of the time. The wisest may err, and there can be no doubt that, even when the greatest care is exercised, an erroneous opinion may occasionally be supported or a faulty judgment passed. Should this occur, THE JOURNAL would be the first to regret it, and it would seize the earliest opportunity to correct it. Its readers may rest assured, however, that no pains are spared to prevent the expression of opinions other than those which represent the sanest medical thought of the day.

One of the subjects in which the growth of our conceptions has been extremely slow, but about which, to-day, our real knowledge far outruns the general professional recognition of it, is that which has to do with the origin, fate and insignificance of uric acid in the body. THE JOURNAL has, on several occasions, called attention to progress in knowledge in this field; it has warned against many of the fallacies which persist, and it has urged the profession to revise views which, though long taught, have been proved to be without firm foundation. The false ideas concerning the mode of formation of uric acid in the body, its decomposition and its pathologic significance have become so deeply rooted, not only in the professional mind, but to a certain extent in the mind of the laity, that it is unusually difficult to eradicate them. The perpetuation of erroneous ideas has been helped no little by various facile publications wherein, doubtless with good intentions and assuredly with great enthusiasm, doctrines have been advocated which are based partly on faulty or mis-

interpreted observations of others, partly on unskilled and non-scientific personal experiments. When such ideas happen to harmonize with the interests of an unbridled commercialism[1] which floods the country with highly colored and sensational reports of marvelous cures by so-called antilithics and uric-acid solvents, it is easy to understand how the attempt may be made by those who have tested interests to prolong the drowsiness of the profession and the laity, and how any effort made to awaken the somnolent may excite antagonism.

A considerable body of definite facts has now been established concerning uric acid. We really know a great deal about its origin, the transformations which it undergoes and the way it is excreted. We are beginning to know something of its significance, though far less, it must be admitted, than many people imagine. It is our intention to re-

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1. Since this was written THE JOURNAL has received a letter from a firm which has been advertising a "uric-acid solvent." This letter is a reply to a circular sent out by the advertising department; it bears so directly on the point mentioned that we quote a part of it: "Should we place an 'ad' with you, it would be to exploit a proprietary preparation for the relief and cure of the uric acid diathesis. It has been made apparent to us that it is the avowed policy of THE JOURNAL to discourage the use of all proprietary preparations, and under date of Aug. 20, 1904, THE JOURNAL in an editorial made a very sarcastic, if not unethical, attack on the uric acid diathesis. We concede to any physician the right to his personal opinion on this subject, and to any journal the right to publish any views which may be held by its editors, but when such views tend to discourage the profession in the use of uric acid solvents and eliminants, it certainly impairs the value of its advertising pages as a medium through which the manufacturer of a uric acid remedy may reach the profession.. This is an additional reason why we now decline to use THE JOURNAL through which to advertise ———."

view, thoroughly though succinctly, the mass of work which has been done on the subject. We shall try to sift out the wheat from the chaff, and shall make an effort to distinguish what is the truth from what is mere poetry in this matter. In our next issue we shall begin with a review of the doctrines which have been held regarding the formation of uric acid in the body; in succeeding numbers of THE JOURNAL we purpose taking up the normal fate of uric acid in the tissues, the facts bearing on the localization of the process of uric-acid formation and decomposition, the chemical and physical properties of uric acid and urates, including the conditions of solubility and precipitation, and, finally, the relation of uric acid to pathologic processes.

The literature on the subject is immense. One has only to glance at the collective bibliographies of the subject which have been prepared, for example, those of Wiener,[2] Laquer, Minkowski and Burian and Schur, of which liberal use has been made in preparing the present résumé, to realize the magnitude of the task which a careful historical review necessitates. It would be impracticable as well as undesirable to marshall all the authorities in the review of the subject which we intend to make for our readers; it will suffice if we point out the most important steps which have been taken as knowledge of the subject has advanced. We believe that such a historical presentation, though it will be full of surprises for many, is the best means of making clear to the profession at large the true status of the questions at issue.

2. Wiener, H.: Die Harnsäure Ergebn. d. Physiol. I Jahrg., I Abth., 1902., pp. 555-650.

CHAPTER II.

DISCOVERY OF URIC ACID AND EARLY THEORIES CONCERNING IT.

Discovery of Uric Acid by Scheele—Early Chemical Studies of the Substance—Medical Observations—Theories of an Origin from Imperfect Oxidation of Proteid.

The history of uric acid dates from a year easily remembered by Americans. In 1776 the substance was discovered by Karl W. Scheele as the constituent of a concrement, and in the same year T. Bergman found it in a stone from the bladder. Soon after it was recognized as a normal ingredient of the urine; it was fated to become the object of a long series of studies. Pure chemists busied themselves with it for a time, Fourcroy (1793) finding urea among its decomposition products, and Wöhler and Liebig (1838), showing that it is closely related to allantoin, urea and alloxan. The majority of the earlier studies on uric acid were undertaken by medical men, and one of the most interesting features of medical research during the past hundred years is the patient but tortuous course followed by those who had as their object the determining of the mode of formation of uric acid in the body. At times the pursuit seemed to be utterly futile, so ignorant were those engaged in it of the direction it should take; more than once it was necessary, to use a sportsman's expression, to "hunt change," to take a fresh scent, as it were, and to seek in an entirely new quarter.

The relationship of uric acid to urea naturally suggested a similar origin for the two substances,

and the earliest theories took it for granted that uric acid, like urea, is a product of proteid metabolism. Since uric acid yields urea as one of its oxidation products, two hypotheses seemed plausible—either all proteid on oxidation to urea passes at some time or another, through a uric-acid stage, or proteid is normally oxidized directly to urea, but under certain pathologic conditions to uric acid instead. In case either hypothesis were true, a fault of oxidation would account for the appearance of increased amounts of uric acid.

Thus Lehmann, in his "Physiological Chemistry," published in 1853, advanced the first hypothesis, assuming that uric acid stands a rung higher on the ladder of descending proteid metabolism than does urea. This view was accepted by many, and the idea became prevalent that an increased excretion of uric acid must be due to disturbances of the circulation or respiration leading to interference with the normal oxidizing processes of the body. Feeding experiments (Neubauer, 1856; Meissner, 1868; Weintraud, 1896, and Spiegelberg, 1898) demonstrated that urica acid in dogs or human beings is given off largely as urea in the urine, one study showing that not more than 5 per cent. of the uric acid fed reappears unchanged in the urine. Haig (1894) asserted that, feeding small amounts of uric acid to healthy men, he could demonstrate prompt and complete excretion as such in the urine, but he is alone in this as in so many observations which contradict the work of other investigators. Of course, the fact that uric acid, like other nitrogenous substances, burns in the body to urea, is no proof that all urea goes

through a uric-acid forestage, and investigators were soon to learn this.

The first hypothesis received strong support from Bartels[3] (1866), who sought evidence in its favor in clinical experience, or rather, who looked for facts that were not out of harmony with the hypothesis. He laid emphasis on the "relative" amount of oxygen available; if there were "relative" insufficiency of oxygen, uric acid, he thought, instead of urea is formed. Thus in certain fevers, like those in pneumonia or accompanying circulatory disturbances, there might be increase in uric-acid formation owing to "relatively" insufficient respiration. Excess of uric acid in leukemic urine he cited as evidence of his view. Virchow had called attention to this increase in uric acid in leukemia as early as 1847, and regarded it as due to imperfect oxidation.

In this connection it is of great interest to note that Scherer,[4] as long ago as 1851, had found hypoxanthin in the spleen and in the blood in leukemia, and had put forward the theory that leukemia is due to a sort of hypersecretion of the spleen. Five years later he found both hypoxanthin and uric acid in the blood in leukemia. The chemical relations of hypoxanthin and uric acid were beginning to be known, and a hypothesis that the spleen is the source of uric acid gained credence for a time, Ranke[5] marshaling as arguments in its

3. Bartels: Untersuchungen über die Ursache einer gesteigerten Ausscheidung der Harnsäure in Krankheiten, Deutsches Arch. f. klin. Med., vol. i, 1866, p. 13.

4. Scherer: Untersuchungen über das Blut bei Leukämie, Verhandl. d. phys. med. Gesellsch. z. Würzburg. vol. ii, 1851, p. 321.

5. Ranke, H.: Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen München, 1858.

favor, (1) the increase of uric-acid excretion with accompanying splenic swelling during digestion; (2) the increase of uric acid in leukemia; (3) the presence of uric acid in the splenic juice; and (4) the action of quinin, which reduces the size of the spleen and diminishes uric-acid excretion. The possibility of an origin of uric acid from hypoxanthin—excessively interesting considering our present knowledge of the purin bases—seemed to threaten the view that is derived from proteid, until some one suggested that hypoxanthin might come also from proteid and be simply a still earlier forestage of urea. Moreover, Bartels' authority was so great that his conception was the dominant one in the minds of medical men for a long time.

Telling blows against Bartels' view were struck later when it began to be shown (1) that conditions which diminish oxidation or interfere with respiration are not necessarily associated with increased uric-acid excretion; and (2) that in leukemia, where uric-acid excretion is sometimes increased, there is no evidence that the oxidizing processes are diminished. Senator (1868) constricted the thorax of dogs and rabbits, and got increased uric-acid excretion in only two out of many cases; Naunyn and Ries (1896) did not find the uric-acid excretion increased in anemia produced experimentally; Pettenkoffer and Voit (1869) showed that nitrogenous and carbon-dionid equilibrium are maintained in leukemia in spite of uric-acid increase, and finally in 1891, Kraus and Chvostek and in 1893, Bohland and Geppert proved that there is absolutely no decrease in the oxygen-intake, nor any decrease in the output of carbon dioxid, in cases of leukemia.

It can be seen, therefore, how it came about that some of the oldest conceptions regarding the formation of uric acid had to be given up. These old views have had a sort of recrudescence, however, from time to time, as will be pointed out further on, when we come to deal with the ideas which supplanted them.

CHAPTER III.

PROOF OF THE ORIGIN OF URIC ACID FROM NUCLEIN.

Discrediting of Idea of Origin from the Oxidation of Proteid—Suggestion of an Origin from Xanthin Bases—Development of Our Knowledge of Nuclein by Miescher and Kossel — Errors of Stadthagen — Mares' Hypothesis—Demonstration by Horbaczewski of the Origin from Nuclein—His Errors.

It has been seen how the hypothesis that uric-acid formation is due to an oxidation of proteid, which stops short of urea, gradually came to be discredited. The keen Salkowski, in 1870, had pointed out that if the uric acid in leukemia is due to faulty oxidation, other incomplete oxidation products must also be present. Those most likely to occur would be oxalic acid and allantoin, but careful studies of the urine in leukemia revealed no increase in these compounds. Salkowski, in 1871, therefore, rejected Bartels' conception and inclined to view with favor Ranke's hypothesis that uric acid is derived from xanthin bases and the spleen. Against this was the observation that xanthin bases appeared to occur in only very minute quantities in the tissues, and, further, that feeding experiments made with xanthin on dogs (an unsuitable animal, as will be seen) caused no increase in uric-acid excretion.

About this time there developed that remarkable series of researches which led to our modern knowledge of the nucleins and their cleavage products—researches which, as they were destined to exercise an important influence on uric-acid studies, must

here be briefly referred to. Miescher, in 1874, working on salmon sperm, had isolated nucleinic acid, and had shown that xanthin bases are formed when it is decomposed. Kossel, 1879, took hold where Miescher was all too early compelled to leave off, and showed that the xanthin bases, namely, xanthin, hypoxanthin, adenin and guanin can be obtained from nuclein; they are not present as free bases in the nuclein, but in organic union in the nucleinic acids. Kossel,[6] in 1881, immediately recalled the old ideas of Scherer and Ranke, and suggested again that the xanthin bases might be forestages of uric acid. The main argument to the contrary, as we pointed out above, had been the sparsity of xanthin bases in the tissues, but Kossel showed that if the organically combined bases be considered, the amounts present, especially in organs like the spleen, liver and kidney, are large. A year later[7] he emphasized in this connection two facts: (1) that the muscles of those animals (birds and reptiles), whose chief metabolic end product is uric acid, are much richer in hypoxanthin than those of mammals; and (2) that in leukemia the nuclein bases in the blood are increased. It is not surprising, therefore, that experimental feeding of the xanthin bases was again resorted to (Baginsky, 1883); but the results left the matter in doubt, and the problem was not to be easily solved.

An important paper by Stadthagen,[8] in 1887,

6. Kossel, A.: Ueber die Verbreitung des Hypoxanthins im Tier- und Pflanzenreiche, Ztschr. f. physiol. Chem., vol. v, 1881, p. 267.

7. Kossel, A.: Zur Chemie des Zellkernes., Ztschr. f. physiol. Chem.. vol. vii, 1882, p. 7.

8. Stadthagen: Ueber das Vorkommen der Harnsäure in verscheidenen tierischen Organen, ihr Verhalten bei der Leukämie und die Frage ihrer Entstehung aus den Stickstoffbasen, Arch. f. path. Anat., etc., Berl., vol. cix, 1887, p. 390.

reported experiments on the feeding of xanthin to dogs, with negative results, so far as an increase in uric acid was concerned. Stadthagen was of the opinion for a time that the nucleins of the food are split sometimes with formation of xanthin bases, at other times with formation of uric acid. He thought it possible that when xanthin bases are once formed from nuclein there can be no formation of uric acid. He therefore fed nuclein directly to dogs with the hope of finding the uric acid increased; the results were, however, negative, though Stadthagen suggested that this might be due to the fact that the nucleins of food are "dead" and may behave differently in metabolism from the nuclein of living cells. This investigator finally, apparently, returned to the old view that uric acid is derived from proteid. His studies had led him to the belief that an origin from nuclein or xanthin bases can not be proved. It seemed to him positively demonstrated (1) that an increase of uric acid is absolutely dependent on the proteid-intake (irrespective of nuclein or xanthin bases), and (2) that uric acid, so abundant in children, must be derived in them from the casein of milk which contains no xanthin bases.

The fallacy of Stadthagen's reasoning is obvious. In the first place, careful experiments have shown that uric-acid excretion is completely independent of the general nitrogen-metabolism.[9] Haig had asserted, it is true, that uric acid and urea are always formed in the same proportion (1:33); this view was entirely arbitrary in its origin, and Haig tried to explain the facts contradicting it by assuming that, when the proportion varies, the dis-

9. Salkowski, 1889, von Noorden, 1893.

crepancy is due not to differences in formation of uric acid, but to increase or diminution in the alkalinity of the blood, with correspondingly increased diminished solubility and elimination of uric acid in the urine. Herringham and Davies, in 1891, showed that the excretion of uric acid varies independently of the blood alkalescence as determined by titration, and a year later Herringham and Growes stated that experiments proved that uric-acid excretion is independent of the ammonia excretion in the urine (which they regarded as a measure of the latent acidity). A review of the various experiments "after the event" shows that the investigators who found a definite dependence of uric acid excretion on proteid-intake had used almost exclusively meat as food in the experiments; where other proteids were administered such dependence was not found to exist. In the second place, Stadthagen was wrong, as Wiener points out, in assuming that the formation of uric acid on a nuclein-free diet (such as milk fed to young infants) makes its origin from xanthin bases or nuclein impossible, for it has been proved that animal cells are capable of manufacturing nucleins from other nitrogenous substances,[10] and this synthesized nuclein may serve as a source of uric acid.

In 1888 Mares put forward the hypothesis that uric acid is a product of the activity of the cell-protoplasm, "of that chemical process which forms the basis of cell-activity." While urea, according to Mares, arises directly from the decomposed proteids of the food, uric acid, he thought, is formed only indirectly from the proteids of food, through

10. Tichimiroff, 1885, Kossel, 1886, Burian and Schur, 1897.

gradual transformation of the organized proteids of the body cells.

The time had now come for a very important discovery. It had remained for Horbaczewski,[11] in 1889, to establish with certainty the direct relation of uric acid to the nucleins. He squeezed spleen pulp, mixed it with defibrinated blood, passed air through it and found that large amounts of uric acid are formed. He believed, therefore, that the forerunner of the uric acid exists in the spleen, and that this forerunner, probably nuclein or one of its cleavage products, yields uric acid on oxidation. Later he isolated nuclein from the spleen and prepared uric acid directly from it; in a similar manner he made uric acid from the nuclein derived from other organs, and these findings, with slight modifications, have been controlled and confirmed by Giacosa (1891), Spitzer (1899), and others. Horbaczewski next resorted to feeding experiments, using rabbits and human beings instead of dogs for the tests, and found an increase in uric acid two hours after the administration of nuclein. All subsequent observers confirm this origin of uric acid from nuclein.

In spite of the fact that Horbaczewski had made a very important discovery, he unfortunately soon strayed into a wrong path. He assumed, without adequate basis, that only the nucleins of leucocytes take part in uric-acid formation, and denied the direct relation of other nucleins to the substance. With this phase of the subject we shall deal in the next chapter.

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11. Horbaczewski: Untersuchungen über die Entstehung der Harnsäure im Säugetierorganismus, Monatsshefte f. Chemie, vol. x, 1889, p. 624.

CHAPTER IV.

URIC ACID ARISES FROM THE NUCLEIN OF ALL THE BODY-CELLS—NOT SIMPLY FROM LEUCOCYTIC NUCLEIN.

Horbaczewski's Erroneous Theory of an Exclusive Origin from Leucocytic Nuclein — Persistence of this Theory Among Medical Men Despite Conflict with Facts—Hypothesis Regarding Excretion of Alloxuric Bodies—Faulty Method of Krüger and Wulff—Fallacies of Horbaczewski's Hypothesis—Evidence of Origin of Uric Acid from all Nucleated Cells—Views of Mares.

Horbaczewski, as we have pointed out, demonstrated the very important fact that uric acid may be derived from nucleins, but went off at a tangent in maintaining that it does not come from all nucleins, but only from the nucleins of leucocytes. His arguments, it must be admitted, sounded plausible enough. He asserted that his studies showed, as a rule, a parallelism between leucocyte counts and uric-acid excretion. Where the parallelism failed he explained the discrepancy by assuming a class of leucocytoses without leucocytic destruction. The blood of children contains more leucocytes than that of adults and this, he believed, accounts for the relatively great excretion of uric acid in the former. Further, he brought the increased excretion of uric acid after eating, especially after a meat diet, into relation with the digestive leucocytosis. Feeding nucleins increases uric-acid excretion, but so convinced was he of his new view, that he assumed that nucleins fed act only indirectly by first producing a leucocytosis. Quinin diminishes leucocytosis, accordingly Hor-

baczewski thought it diminishes uric-acid excretion. Pilocarpin, he stated, increases both uric-acid excretion and the leucocyte count.

Medical men for a time were ready to follow Horbaczewski. Hypnotized, as it were, by the brilliant proof of the origin of uric acid from nuclein, they were eminently susceptible to any suggestion that came from him. Thus Horbaczewski's theory of an origin of all uric acid from leucocytic nuclein alone, despite its flimsy foundation, met with remarkably general approval and acceptance. Many confirmatory reports of uric-acid determinations running parallel to leucocytoses were made; discordant findings were lightly explained away.

A new impetus to work on the urine was given in 1895 by Krüger and Wulff, who introduced a method for easily and quickly determining the amount of alloxuric bodies (uric acid plus xanthin bases) excreted. The idea gained ground that some of the discrepancies in the results above referred to might depend on the fact that in the decomposition of leucocytic nucleins both xanthin bases and uric acid are formed and that the relative amounts of these vary under different conditions of metabolism; if the total alloxuric bodies could be easily determined a parallelism of their excretion with the leucocyte count might, it was hoped, prove to be more constant than that of the uric acid alone. Leukemia was the disease which invited a special investigation in this regard, and between 1894 and 1898 we find a number of researches bearing on this subject. The results were, however, very conflicting, and in 1897 Hüppert and, in the same year, independently, Salkowski proved

the total unreliability of the method of Krüger and Wulff; no importance, therefore, is to be attached to results based on its application to the study of our subject unless they are also supported by more accurate analytical methods.

Even when more exact methods were employed, very contradictory results were obtained by equally good observers. In the study of pneumonia, especially, there was no concordance. While some maintained that the uric-acid excretion is increased at the height of the leucocytosis, others asserted that it is only after beginning absorption of the exudate that uric acid is excreted in larger amounts. The studies of Kühnau[12] were among the most elaborate. He corroborated Horbaczewski's view as a result of his examination of the metabolism in pneumonia and pleurisy and where a leucocytosis appeared with no corresponding increase in uric-acid excretion he even thought it probable that this is to be explained by assuming that the leucocytes wander gradually back into the tissues without undergoing destruction.

A modification of Horbaczewski's views was suggested by Dunin and Nowaczek.[13] These investigators denied that the increased uric-acid excretion

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12. Kühnau, W.: Experimentelle und klinische Untersuchungen über das Verhältniss der Harnsäure-ausscheidung zur Leukocytose. Ztschr. f. klin. Med., vol. xxviii, 1895, p. 534; Ueber das Verhalten des Stoffwechsels und der weissen Blutelemente bei Blutdissolution. Deutsche Arch. f. klin. Med., vol lviii, 1897, p. 339; see also Kühnau und Weiss; Weitere Mittheilungen zur Kenntniss der Harnsäureausscheidung bei Leukocytose und Hypoleukocytose, sowie zur Pathologie der Leukämie. Ztschr. f. klin. Med., vol. xxxii, 197, p. 482.

13. Dunin, T., u. Nowaczek, S.: Ueber Harnsäureausscheidung bei croupöser Pneumonie. Ztschr. f. klin. Med., vol. xxxii, 1897, p. 1.

in pneumonia keeps pace with the increase of leucocytes in the blood, but attributed it solely to the absorption of the resolving exudate, and Carlyle Pope's findings in 1899 may be similarly interpreted.

Richter,[14] in 1895, had published a long series of observations which indicated that no constant relation between leucocytosis and uric-acid excretion can exist; in spite of his results he still leaned more or less on Horbaczewski's views.

Enough has been said, perhaps, to show what a sorry state the subject was in at this time. Some workers felt sure that the presence of a leucocytosis in the peripheral blood indicates an increased destruction of leucocytes; others were equally sure that a hypoleucocytosis is a certain indication that leucocytes are being destroyed, both sides apparently forgetting two important facts (1) that the number of leucocytes existent at any time represents the algebraic sum of the leucocytes manufactured and the leucocytes destroyed, and (2) that the number of leucocytes present in a peripheral vessel often depends on abnormal distribution rather than on abnormal production or destruction.

The factor of distribution of leucocytes in relation to leucocytosis was emphasized by Rieder in 1892 and later by Goldscheider and Jakob in 1894. Thayer and Billings at the Johns Hopkins Hospital showed how cold baths given to typhoid patients temporarily lead to accumulations of leucocytes in

14. Richter, P. F.: Ueber Harnsäureausscheidung und Leukocytose. Ztschr. f. klin. Med., vol. xxvii, 1895, p. 290.

the cutaneous blood vessels, and Bohland,[15] in 1899, found that atropin causes hypoleucocytosis in peripheral vessels, while the capillaries of the lungs are dilated and crowded with leucocytes; pilocarpin causes diminution of the leucocytes in the lung capillaries. Pilocarpin, it is said, increases uric-acid excretion, while atropin does not. His explanation was that pilocarpin increases the decomposition of nuclein, in spite of the absence of leucocytosis, and so more uric acid is excreted.

The sum of all these researches shows that while destruction of leucocytes in the body leads to increased uric-acid excretion, the number of leucocytes in the peripheral vessels is no gauge for the amount of leucocyte destruction going on nor for the amount of uric-acid formation. Moreover, a whole series of conditions has been studied in which there is increased uric-acid excretion without leucocytosis or evidence of leucocytic destruction. In many of these conditions nucleated cells other than leucocytes are destroyed. Again, as Minkowski[16] states, there is good reason to believe that an increased function of nucleated cells, without actual cell destruction, may be sufficient to augment nuclein cleavage and uric-acid formation. Indeed, it is not impossible, as Melis-Schirru[17] suggests, that increased uric-acid excretion and leucocytosis may be due to one and the same cause. If the ac-

15. Bohland: Ueber die Einwirkung der Hydriotica und Antihydriotica auf den Leucocytengehalt des Blutes. Centralbl. f. inn. Med., vol. xx, 1899, p. 361. Ueber den Einfluss einiger Arzneimittel auf die Bildung und Ausscheidung der Harnsäure. Münch. med. Wchnschr., vol. xlvi, 1899, p. 505.

16. Minkowski, O.; Ueber Leukämie und Leukocytose. Verhandl. des xvii. Kongr. f. inn. Med., 1899, p. 158.

17. Melis-Schirru: Sulla genesi dell'acido urico. Centrabl. f. inn. Med., vol. xx, 1899, p. 1042.

tivity of the hemopoietic organs be increased from any cause, the first expression may be augmented nuclein metabolism; if the activity be still further exaggerated, leucocytosis results.

Strangely enough, as far back as 1892, Mares[18] had recognized the fallacies of Horbaczewski's arguments and made their insufficiency clear. At that time he accepted an origin from nuclein, but urged (1) that uric acid may be formed by a vital chemical process through gradual metabolic decomposition of nuclein instead of by the passive process of cell-death and nuclear destruction, and (2) that the nuclein of any of the body-cells, and not simply that of the leucocytes, may give rise to uric acid. Horbaczewski's star was, however, so in the ascendant at that time that but little attention was paid to these keen observations of Mares. And even Mares did not see the whole truth, for he denied the direct transformation of the nucleins of the food into uric acid; as to the possibility of the latter process we shall have something to say in a succeeding section.

18. Mares: Zur Theorie der Harnsäurebildung im Säugetierorganismus. Monatsch. f. Chem., vol. xiii, 1892, p. 101.

CHAPTER V.

DEMONSTRATION THAT URIC ACID ARISES ALSO FROM THE NUCLEINS AND XANTHIN BASES OF INGESTED FOOD; ORIGIN OF THE CONCEPTION OF EXOGENOUS AND ENDOGENOUS PURINS.

Truth and Error in Mares' Views — Increased Uric-Acid Excretion After Ingestion of Foods Rich in Nuclein or in Xanthin Bases—Process in Man Varies from that in Dogs—Definition of Term "Purin Bodies"—Endogenous and Exogenous Purins of Burian and Schur—Relative Amounts of These—Their Sources.

Mares' hypothesis assumed that all uric acid excreted comes from the nucleins of the cells of the body; it denied any direct origin from the nucleins of the food.

The incorrectness of this assumption has since been shown by many researches. Thus it was soon demonstrated that foods rich in nuclein or in xanthin bases exercise a powerful effect on the excretion of uric acid (Horbaczewski, Richter, Weintraud, Lütje). A difference, however, in the action of the nucleins of individual foods is discernible. Umber showed that while the feeding of thymus and liver increases uric-acid excretion, the feeding of brain and kidney, which are almost equally rich in nucleins, does not increase it, at any rate to the same extent; the mode of chemical union in the various nucleinic acids, therefore, Umber thought, can be of great importance. Similar experiments were made by P. Mayer, Jacob and Bergell, Rosenfeld and Orgler, Carlyle, Pope and Minkowski. It must be considered as established that nuclein in the food can increase uric-acid excretion.

Despite these researches, the reason for increased uric-acid excretion after the eating of meat still remained obscure, for meat, Kossel showed, contains but little nuclein; further, it had already been proved that there is no direct relation between proteid intake and uric-acid excretion. That meat eating does significantly increase the uric-acid output had been repeatedly demonstrated (Strauss, Smith and Jerome, Zagari and Pace, Sivén). The explanation came with the discovery by Kossel of the existence of an abundance of free xanthin bases in meat, and with the bringing of the proof by Burian and Schur, that of the 0.06 per cent. of purin bodies present in meat, no less than 0.045 per cent. are in a free state. If free xanthin bases can give rise to uric acid, as would seem probable, since the synthetic studies of Emil Fisher have shown their near relations to one another chemically, the increased uric-acid excretion after meat eating is easily accounted for.

And yet, the older experiments, it will be recalled, indicated that the feeding of free xanthin bases alone does not increase uric-acid excretion It was time that that observation should be subjected again to an experimental test, and this work was undertaken by Minkowski.[19] His studies showed that the feeding of xanthin bases, especially hypoxanthin, leads in man to marked increase of uric-acid excretion. The earlier experiments, which had been negative, had been made chiefly on dogs; Minkowski discovered that in the dog the xanthin

19. Minkowski, O.: Ueber den Einflus der Leber-Exstirpation auf den Stoffwechsel, Arch. f. exper. Path. u. Pharmak., vol. xxi, 1886, p. 89; Untersuchung zur Physiologie und Pathologie der Harnsäure bei Säugetieren, ibid., vol xli, 1898, p. 375.

bases fed are excreted not as uric acid, but as allantoin; this explains how the idea had arisen that the feeding of xanthin bases does not increase uric-acid excretion. This proof of the possibility in man of a direct transformation of the xanthin bases of the food into uric acid independently of any intermediation of the leucocytes of the body, marks the next important step forward in the progress of knowledge in connection with our subject.

It had by now become perfectly clear that the uric-acid excretion can be derived from at least two sources—first from the nucleins of the cells of the body itself, and second, from the nucleins and xanthin bases of the ingested food. From this time on, it became customary to speak of the excretion of "purin bodies" (xanthin bases plus uric acid) in the urine, rather than simply of the excretion of uric acid. Since Emil Fischer had shown the existence of a "purin-nucleus" common to the molecules of uric acid and of all the xanthin bases, Burian and Schur[20] refer to that portion derived from the metabolism of the body cells as "endogenous" urinary purin bodies, and to that portion derived from the nuclein and xanthin bases of the food as "exogenous" urinary purin bodies.

An interesting attempt was made by Burian and Schur to determine more exactly the actual relative amounts of endogenous and exogenous purin bodies. They believed that by estimating the purin content of the urine of well-fed human beings, whose diet was kept free from purin bodies, they had determined the amount of endogenous purin bodies excreted. Their findings indicated

20. Burian, R., and Schur, H.: Ueber die Stellung der Purinkörper im menschlichen Stoffwechsel, Pflüger's Archiv, vol. lxxx, 1900, p. 241, and vol. lxxxi, 1901, p. 239.

individual differences for this value. The increase in the amount of purin bodies excreted when nucleins or xanthin bases are fed to the same individual indicates, they thought, the amount of exogenous purin bodies created. The latter amount, they believed, is dependent wholly on the quantity and quality of purin bodies fed. They asserted that 50 per cent. of the hypoxanthin ingested as food (either free hypoxanthin or that combined in nuclein) is given out in the form of purin bodies in the urine, while only 25 per cent. of the adenin ingested is excreted as urinary purin.

Extremely valuable as have been the contributions of Burian and Schur to the physiology and pathology of uric-acid excretion, they have, it appears, gone too far in their later assumptions. The matter is not so simple and diagrammatic as their work would lead us to believe. Some of the objections to their views have been well formulated by O. Löwi.[21] He points out that it is really impossible by our present methods to determine accurately how much of the purin bodies excreted is endogenous and how much is exogenous in origin.

In all probability, the endogenous purin bodies can be derived from several different sources. Thus under physiologic conditions it seems probable that in mammals they are derived chiefly from the nuclein metabolism of the body cells and, principally, of those body cells which undergo most active chemical changes, namely, the cells of the secreting glands and of the muscles. A further possible source of endogenous purin bodies, even in mammals, is by way of direct synthesis. So much

21. Löwi, O.: Beiträge zur Kenntniss des Nukleinstoffwechsels, Arch. f. exper. Path. u. Pharmak., vol. xliv, 1901, p. 1, and vol. xlv, 1901, p. 157.

attention had thus far been directed to the origin of uric acid by the oxidation of complex compounds that but little consideration had been given to the possibility of its formation in the organism by the union of simpler bodies. We shall turn in our next chapter to a consideration of the possibility of such a synthetic origin of uric acid.

CHAPTER VI.

URIC-ACID FORMATION IN MAN CHIEFLY OXIDATIVE, BUT POSSIBLY ALSO SYNTHETIC.

Oxidative Origin Manifoldly Proven—Question of Origin by Synthesis—Feeding Substances which May Be Synthesized to Uric Acid in the Test-tube—Collateral Evidence Suggestive of Synthesis—Appeal to Comparative Physiology—Synthetic Formation of Uric Acid in Birds and Reptiles—Minkowski's Studies of Synthesis in Bird's Liver—Confirmation and Extension by Wiener — Probability of Some Synthetic Formation in Man.

Slowly but surely, as we have seen, the truth concerning the formation of uric acid in the body was being found out. An origin from the metabolism of the nuclein of the body cells had been established; the possibility of the formation of uric acid directly from the nucleins or xanthin bases of the foods had been definitely demonstrated; and, as we hinted in the concluding paragraph of our last article, the possibility of a third mode of formation, namely, through synthesis of simpler chemical compounds, began to be considered.

Efforts to solve the problem as to whether or not synthetic formation of uric acid occurs in the body were made in various ways. Some tried to increase uric-acid excretion by feeding substances from which uric acid can be manufactured synthetically outside the body; others by feeding substances which are known to be derived from the decomposition of uric acid within the organism. The earlier experiments of this sort were negative. Horbaczewski, in 1882, tried feeding experiments with glycocol, but got no marked increase in uric-acid

excretion; a similar experiment by Weiss, in 1899, yielded negative results. Minkowski, in 1898, fed lactic acid and urea to dogs in the hope that these bodies might be synthesized to uric acid, but without obvious success. He was led to try the experiment by the fact that in birds from which the liver has been extirpated, the uric acid of the urine is replaced by lactate of ammonia, and, beside, Horbaczewski had synthesized uric acid *in vitro* from trichlorlactic acid and urea. Nor were experiments in which men were fed with these substances more successful (Hermann, 1888; Weiss, 1898).

Despite the discouraging influence of these early attempts at intracorporeal synthesis of uric acid, investigators continued to hope that the proof of the synthetic formation might yet be brought. This hope was fostered by a group of facts which made it seem improbable that the total formation of uric acid in the body can be accounted for without synthesis. Thus it had been shown that the feeding of glycerin increases the amount of uric acid excreted, and some feeding experiments made with fats and carbohydrates pointed to the probable synthetic formation of uric acid, in certain circumstances. The studies of Hopkins and Hope, in 1898, indicated that the excretion of uric acid after meat-eating occurs earlier and ceases sooner than that of other nitrogen compounds. The increase occurs too quickly to be accounted for by the absorption of nuclein, and, further, is not due to sudden excretion dependent on removal of preformed uric acid rendered more soluble. They thought, therefore, that some substance in meat, which can increase the excretion of uric acid, is absorbed by the stomach. Again, in 1899, Wiener

showed the capacity of isolated organs to synthesize uric acid. Thus the isolated liver of animals is capable of manufacturing uric acid from an alcoholic extract of various organs, even when this extract is free from nuclein and xanthin bases.

It was to comparative physiology, however, that investigators had to turn for help, in connection with the synthesis of uric acid in the animal body. It had long been known that certain animals, like birds and reptiles, excrete most of their nitrogen not as urea, as in mammals, but as uric acid. In these animals the amount of uric acid excreted varies with the amount of food ingested. It sinks in inanition; it is increased in all conditions which augment proteid metabolism. Substances which, when fed to mammals, are oxidized to urea are excreted in birds as uric acid. All these facts indicated that in birds and reptiles synthesis plays an important rôle in uric-acid formation.

A very important publication was made on this subject in 1886 by Minkowski.[22] This investigator on extirpating the livers of birds, found that the nitrogen of the urine was present as ammonia, not as uric acid. And since ammonium lactate was present in the urine, he thought it probable that ammonia and lactic acid are important forestages in uric-acid synthesis, and that this synthesis is effected in the liver in birds. The idea soon gained ground that in the synthesis of uric acid two molecules of urea unite with some atom complex containing three carbon atoms but no nitrogen. Minkowski thought that this non-nitrogenous atom complex is furnished by lactic acid, and his view

22. Minkowski, O.: Ueber den Einfluss der Leberextirpation auf den Stoffwechsel, Arch. f. exper. Path. u. Pharmakol., Leipz., vol. xxi, 1886, pp. 41-87.

received some support through the facts that the feeding of lactic acid to birds increases uric-acid excretion (Wiener, 1902), and that when lactic acid is passed through the isolated bird's liver uric acid is formed from it (Kowalewski and Salaskin, 1901).

In view of the high degree of probability that lactic acid takes part in the synthesis of uric acid in birds, it became important that the process should be more closely examined with special reference to its exact nature. Wiener,[23] in 1902, demonstrated that the administration of glycerin, of various oxyacids, and especially of dibasic acids (of the aliphatic series) containing three carbon atoms, along with urea, increases markedly the formation of uric acid. Laboratory experiments had shown that urea can unite with dibasic acids containing three carbon atoms to form compounds called ureids, and that certain of these ureids can combine with another molecule of urea to form uric acid. While the feeding of any dibasic acid containing three carbon atoms to birds increases the uric-acid formation, Wiener found that, when he used isolated organs, only one dibasic acid, namely, tartronic acid (or its ureid) was effectual. He concluded, therefore, that other dibasic acids or their ureids are transformed into the ureid of tartronic acid in the process of uric-acid synthesis. Thus lactic acid (CH_3-CHOH-COOH), he thinks, is first transformed to tartronic acid (COOH-CHOH-COOH), and later unites with urea to form a ureid (dialuric acid), after which the addition of another urea molecule gives rise to uric acid. When

23. Wiener, H. Ueber synthetische Bildung der Harnsäure im Thierkörper, Beitr. z. chem. Physiol. u. Path., vol. ii, 1902, p. 42.

the liver of the bird is removed, not only is the synthesis of uric acid itself prevented, but, in addition, the oxidation of lactic acid to tartronic acid is interfered with and ammonium lactate appears in the urine

The principal mode of formation of uric acid in birds, then, is by the method of synthesis. Birds, however, do form some uric acid in the way in which it is chiefly formed in mammals, namely, through nuclein metabolism and through the transformation of the nucleins and xanthin bases of the food. We feel confident of this, because even after the removal of the liver in birds a little uric acid is excreted, and the feeding of hypoxanthin to birds deprived of their livers increases the amount of uric acid excreted (von Mach, 1888).

The question of a synthetic formation of uric acid in mammals and man now grew more interesting. If there are two modes of formation of the substance in birds, it would seem very probable that there are also two modes in mammals. On feeding lactic acid or dialuric acid (the ureid of tartronic acid) to human beings, Wiener, in 1902, found a slight but distinct increase in the uric-acid output. Now, since lactic acid is known to be one of the intermediary products of metabolism, he concluded that uric acid, under normal conditions, is synthesized, to a certain extent at least, even in man.

Another possible mode of formation of uric acid by the chemical union of similar bodies is conceivable. It had been known since Strecker's work (1868) that uric acid can be broken up into glycocoll, carbon dioxid and ammonia. Maly suggested, as early as 1872, the possibility of a syn-

thetic production of uric acid in the body from glycocoll, and ten years later Horbaczewski showed that, at any rate *in vitro,* glycocoll and urea can be synthesized to uric acid.

A beautiful experiment in physiologic chemistry, the synthesis by the kidney of benzoic acid and glycocoll with formation of hippuric acid, has for some time been known; it stimulated the imagination of investigators, and the relative excretion of hippuric acid and uric acid began to be watched. Weiss,[24] in 1898, asserted that after eating fruit the uric acid of the urine is decreased and the hippuric acid increased. He sought an explanation in the presence of China acid (tetraoxyhexahydrobenzoic acid) in the fruit, and assumed that the China acid in the body becomes changed into benzoic acid, and so prevents the synthesis of uric acid from glycocoll. If this idea of Weiss were correct, then, as Wiener points out, all acids which can unite with glycocoll in the body should have the same effect, and benzoic acid itself should act even more definitely than China acid. On administration of benzoic acid, however, though the hippuric acid is increased, there is no decrease in uric-acid excretion (Weiss, Lewandowsky); moreover, salicylic acid, which pairs easily with glycocoll and, according to Weiss' theory, should diminish uric-acid excretion, is held by a whole series of observers to be one of the few drugs which increases it. It has also been shown that hippuric-acid formation goes on entirely independently of uric-acid formation (Weintraud, 1900), so that the doctrine of a competition for the available glycocoll can scarcely

24. Weiss, J.: Beiträge zur Erforschung der Bedingungen der Harnsäurebildung, Ztschr. f. physiol. Chem., vol. xxv, 1898, p. 393.

longer be held. The question of the synthesis of uric acid from glycocoll in the body, for the present, must be left open.

That uric acid is formed, however, to a certain extent synthetically in man and mammals, we think, must be regarded as probable, even though the details of the combining processes are not yet fully understood. Minkowski's and Wiener's ideas have much in their favor, and we should not be surprised if the proof were ultimately brought that the synthesis of uric acid in the liver results from the union of tartronic acid, successively, with two molecules of urea. We are irresistibly led to the conclusion, therefore, that uric acid in the vertebrate animal body is formed both by an analytic (oxidative) and a synthetic process, the forter in birds and reptiles. It is only fair to say, however, that some excellent physiologic chemists doubt a synthetic origin of uric acid in man.

CHAPTER VII.

DESTRUCTION OF URIC ACID WITHIN THE BODY.

Uric-acid Excretion Not an Exact Index for Uric-Acid Formation—Amount Excreted Affected Also by (1) Retention. (2) Decomposition—Retention in Health and in Disease—Destruction Involves Uric Acid of Both Exogenous and Endogenous Origin—Modes of Cleavage of Uric Acid—Glycocoll as an End-Product—Decomposition Probably Due to a Ferment.

In discussing uric-acid formation we have gone thus far on the general assumption that uric-acid excretion is an index therefor. We have followed this plan in order not to make the discussion too complex, but it must now be pointed out that uric-acid formation and uric-acid excretion do not always go on parallel to each other. Uric-acid excretion depends not on uric-acid formation alone, but probably on two other factors: First, on retention due to the difficult solubility of the substance; second, on the decomposition of uric acid, once it has been formed inside the body.

While uric acid is a difficultly soluble substance and is easily precipitated from solution, in normal circumstances the factor of retention from this cause probably influences uric-acid excretion very little. Haig, it is true, in order to bolster up his theoretical conceptions when the facts contradicted them, has made a great point of uric-acid retention. He brings forward no convincing evidence in favor of his view, and other investigators do not support him. In disease, on the other hand, there may be marked retention of uric acid and precipitation in the tissue; under these conditions

it would be fallacious to suppose that the amount of uric acid excreted is an index to the amount formed. The literature on gout shows how prone physicians are to fall into this error, and the conflicting theories of gout have largely arisen as a result.

Much more important in normal conditions is the fact that a certain amount of uric acid is destroyed in the body after it is formed. We have known for more than fifty years[25] that most of the uric acid fed as such is transformed in the body to urea, and recently this fact has been established beyond doubt.[26] Different animals behave somewhat differently in this regard, dogs converting more of the uric acid to urea than rabbits.[27] Newborn dogs, on the other hand, do not decompose the uric acid to any extent.

Since uric acid introduced as such is largely destroyed in the organism, it was natural, reasoning by analogy, to think that uric acid formed as an intermediary product of metabolism in the body, should undergo a similar decomposition. Many researches have been made to test this point, with conflicting results, Loewi denying such a decomposition, Burian and Schur maintaining it. As far as we can judge, the latter investigators are right. One experiment of theirs makes their idea very probable. On injection of a given amount of uric acid into an animal, the same amount of uric

25. Wöhler u. Frerichs: Ueber Veränderungen, welche namentlich organische Stoffe beim Uebergang in den Harn erfahren, Ann. d. Chem. u. Pharm., lxv, p. 335, 1848.

26. Weintraud, W.: Ueber Harnsäure im Blut und ihre Bedeutung für die Entstehung der Gicht, Wiener klin. Rundschau, x, 1896, Nos. 1 and 2.

27. Ebstein u. Nikolaier: Ueber die Ausscheidung der Harnsäure durch die Niere, Virch. Arch., cxliii, 1896, p. 337.

acid is excreted in the urine as when equivalent amounts of purin bases are given to the same animal, either subcutaneously or by the mouth. The most plausible explanation seems to be that the purin bases are converted into uric acid, and that a part of this is destroyed just as when uric acid itself is administered.

According to Burian and Schur, it is possible to calculate from the uric acid excreted in twenty-four hours, the amount which has been formed during this time. Their rule is to multiply the amount excreted by a fraction whose numerator is 100 and whose denominator is that percentage of the purin nitrogen taken in which is given out as uric-acid nitrogen. Reducing this fraction we obtain the so-called integrative factor; in the dog it is 22; in the rabbit, 6; in man, 2.

Besides having proved the decomposition of uric acid of exogenous origin in this way, Burian and Schur believe that they have shown that a similar fate awaits the purin of the uric acid of endogenous origin. Thus the blood of dogs on a purin-free diet, after extirpation of the kidneys, contains no uric acid. This might mean either that the kidneys form uric acid, or that the uric acid in the blood is in a combined state, or that under the conditions mentioned the uric acid formed is destroyed. Now, on excluding the liver from the circulation in such animals, uric acid appears in the blood at once. Thus Burian and Schur believe that in nephrotomized dogs, and probably also in normal dogs, the liver destroys the uric acid of endogenous origin. Further experiments by the same investigators, less well founded, we fear, indicate that the human kidneys, unlike the dog's, has the power of destroy-

ing uric acid, and that the human liver is far less capable of decomposing uric acid than is that of the dog. Burian and Schur reach the general conclusion that the uric acid of endogenous origin is always destroyed, and therefore that uric acid is to be regarded not as a terminal product of metabolism of the purin bodies, but as an intermediary product of that metabolism. We present these conclusions, but are as yet unable to accept them as proved.

The question now arises: What is the exact nature of the decomposition of uric acid in the body, and what are the products of its cleavage? It has been shown by laboratory experiments that uric acid can be broken up *in vitro* in at least three different ways: First, on treatment with concentrated hydrochloric acid, under special conditions, it yields glycocoll, carbon dioxid and ammonia. Second, on treatment with nitric acid, it yields first alloxan and later parabanic acid and carbon dioxid; the parabanic acid then goes to oxaluric acid and later still to oxalic acid and urea. Third, on treatment with permanganate of potash, uric acid is split to allantoin and carbon dioxid, and the allantoin on oxidation yields urea and oxalic acid.

Physiologic chemists have been interested in finding out whether uric-acid decomposition in the body follows any one of the above three routes, or travels along a path of its own. Urea, glycocoll, oxalic acid and allantoin have all been demonstrated in the animal body, and all have at one time or another been supposed to be related to the decomposition of uric acid. It will be noted that no matter which of the three modes of decomposition mentioned above were followed in the body, urea

would always arise, since in the second and third methods urea is formed directly and by the first method the glycocoll would burn to urea; so the evidence of an increased urea formation after feeding uric acid affords no clue as to the way in which the uric acid breaks down. It would take too long here to review in detail the many experiments which have been made to settle this question, but it may be stated that thus far it has not been demonstrated with certainty that either oxalic acid or allantoin is produced in the animal body as a result of the decomposition of uric acid. It has been definitely proved, however, that glycocoll arises in man and animals as a result of the celavage of uric acid.[28] It seems probable, therefore, that when uric acid is decomposed inside the body it undergoes cleavage by the first method described; that is to say, it is split into glycocoll, carbon dioxid and ammonia. The possibility of the occurrence of decomposition by other methods, however, is by no means positively excluded.

Just how the cleavage is brought about is a point which is beginning to be studied. Croftan,[29] as a result of a series of careful experiments, suggests that an albumose-like body loosens the affinities of the uric-acid molecule, and that a nucleo-proteid, acting as an oxygen carrier, facilitates the subsequent oxidation. At any rate, there seems to be a catalyzer that is destroyed by heat concerned in the process. In other words, the destruction of

28. Wiener, H.: Ueber das Glycocoll als intermediäres Stoffwechselprodukt, Arch. f. exper. Path. u. Pharmakol., xl, 1897, p. 313; Ueber Zerzetzung und Bildung der Harnsäure im Tierkörper, ibid., vol. xlii, 1899, p. 375.

29. Croftan, A. C.; Synopsis of Experiments on the Transformation of Circulating Uric Acid in the Organism of Man and Animals, Med. Rec., New York, lxiv, 1903, pp. 6-11.

uric acid is brought about by a ferment. It may be that alcohol and other substances inhibit the action of this ferment and so diminish normal uric-acid destruction.

We have next to consider the exact localization in the body of the processes of uric-acid formation and decomposition. To the work which has been done on this subject we shall refer in the next chapter.

CHAPTER VIII.

LOCALIZATION WITHIN THE BODY OF THE PROCESSES OF URIC-ACID FORMATION AND URIC-ACID DESTRUCTION.

Different Parts of the Body are Variably Concerned in these Processes—Sites of Uric-Acid Formation—Investigation (1) by Studying Metabolism After Excision of Organs, (2) by Quantitative Determination of Uric Acid Present in Different Organs, and (3) by Study of Metabolism in "Over-Living" Organ — Conclusions — Sites of Uric-Acid Destruction—Activity of Ferments in these Processes.

Coincidently with the study of the methods by which uric acid is formed and destroyed in the body, efforts were made to determine the exact localization of these processes. The site of formation of uric acid was one of the earliest points to be studied, and the problem was approached in various ways. At first, certain organs supposedly related to uric-acid formation were removed and the metabolic changes following the operation studied. Thus an idea had early gained ground that uric acid is formed in the kidneys. Zalesky,[30] who was unable to demonstrate the presence of uric acid in the normal blood of birds and snakes, declared that on tying the ureters deposits of uric acid appear first in the kidneys, then in the adjacent lymphatic system and, later, in the blood and in the other tissues. In other words, the deposits gradually spread from the kidenys as a center, and this mode of distribution led him to the firm belief that the kidneys form the uric acid. It was shown

30. Zalesky: Untersuchungen über den uraemischen Process und die Funktion der Nieren. Tübingen, 1866.

later by Meissner,[31] however, that uric acid is present in the normal blood of birds, and other investigators (Chrzonszczewsky, 1866; Colosanti, 1881; Pawlinoff, 1875) proved that the deposition of uric acid and urates does not proceed to regularly from the kidneys as a center as Zalesky had thought; indeed, the findings of these observers rather pointed toward an extrarenal origin of the uric acid. In birds it was shown that local injury to the tissues anywhere often causes a deposition of uric acid, and it seemed likely that the predominance of deposits in and about the kidneys in Zalesky's experiments might fairly be attributed to the trauma

A second mode of ascertaining the site of uric-acid formation consisted in the determination of the quantities of uric acid present in various organs. This was the method followed by Meissner, who, on account of the large amout of uric acid present in the liver of birds, advanced the theory that the liver is the organ in which the substance is built. Others confirmed Meissner's view in that they found much uric acid in the livers of the ox, pig, horse and man. Against this view it was urged first, that only a small amount of uric acid is present in the liver of the dog; second, that uric acid is present in considerable quantities in other organs, like the spleen (Scherer, Ranke); and third, that the presence of uric acid in an organ may mean only its accumulation, not its formation, there.

A third mode of searching for the building place of uric acid was resorted to; certain organs of the

31. Meissner, G.: Beiträge zur Kenntnis des Stoffwechsels im tierischen Organismus, Ztschr. f. rat. Med., vol. xxxi, 1868, p. 144.

body were isolated and the substances from which uric acid can be formed were passed through them. The amount of uric acid formed could then be measured directly, control experiments showing that the uric acid output was not due simply to the washing of preformed uric acid out of the organ. This, or a modification of it, is the method which has been used by Spitzer,[32] Wiener,[33] and especially later by Kowalewski and Salaskin.[34]

Without entering into the details of the various experiments or the discussions to which they have given rise, it may be said that the formation of uric acid by oxidation of nuclein or xanthin bases has been shown to take place in a great many different organs of the body, while the formation of uric acid by the synthetic method occurs chiefly, if not solely, in the liver.

Of equal interest are the studies made to determine the site of uric-acid destruction in the body. The researches of Stokvis (1861), Ascoli (1898) M. Jacoby (1899), Wiener (1899), and Croftan (1903) indicate that various organs destroy uric acid and, indeed, that some of the organs that build it also decompose it. There is marked variability in different animals in this regard; in carnivorous and omnivorous animals it would appear as though the liver, for instance, is actively destructive of uric acid while in herbivorous animals the synthetic

32. Spitzer, W.: Die Ueberführung von Nukleinbasen in Harnsäure durch die Säuerstoffuebertragende Wirkung von Gewebsauszügen, Pflüger's Arch., vol. lxxvi, 1899, p. 192.

33. Wiener, H.: Ueber Zersetzung und Bildung der Harnsäure im Tierkürper, Arch. f. exper. Path. u. Pharmak., vol. viii, 1899, p. 375.

34. Kowalewski, K., und Salaskin, S.: Ueber die Bildung der Harnsäure in der Leber der Vögel, Ztschr. f. physiol. Chem., vol. xxxiii, 1901, p. 210.

production of uric acid would seem to predominate over the destroying power of the organ. Croftan's studies of human tissues indicate that, bulk for bulk, the human kidney destroys more uric acid than the liver, the liver more than the muscles, the muscles more than the spleen and the blood. If one includes the relative bulk of these organs, as compared with the bulk of the whole body, in the calculation, he finds that the muscles destroy most uric acid, next the kidneys, and then the liver, the spleen and the blood.

There is room for much valuable work on the ferments or catalyzers which are responsible for uric-acid formation and for uric-acid destruction. Only a beginning has been made in this direction, but the field is so promising a one that it will be strange if a number of investigators are not soon attracted to it. The work which has already been done has been admirably reviewed by Professor Chittenden of Yale in the Shattuck lecture delivered in Boston in June, 1905. This lecture should be read and carefully studied by all interested in problems of metabolism.*

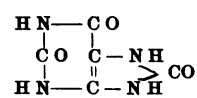
* See also Schittenhelm, A., Ueber die Harnsäurebildung und die Harsäurezersetzung in den Auszügen der Rinderorgane; ein weiterer Beitrag zur Kenntniss der Fermente des Nucleinstoffwechsels. Ztschr. f. physiol. Chem., Strassb., 1905, xlv, 121-151.

CHAPTER IX.

THE STEREOCHEMISTRY OF URIC ACID AND OF SOME OTHER PURIN BODIES. THE URATES AND THEIR SOLUBILITY.

Empirical and Rational Formulæ of Uric Acid—The Purin Ring—Uric Acid as Trioxypurin—Xanthin—Caffein——Adenin—Guanin—Solutions of Uric Acid—Primary and Secondary Dissociation—Effect of Acids and Alkalies on Solubility—Mononatrium Urate—Dinatrium Urate—The So-called "Quadriurate"—Colloidal Solutions of Urates.

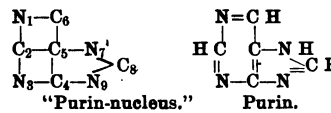
Before going on to a discussion of the conditions of uric-acid formation, uric-acid decomposition and uric-acid elimination in pathologic states it is necessary, in order that the discussion may be intelligible, to review briefly the facts which have been established regarding the chemical nature and physical properties of uric acid and the urates. The empirical formula for uric acid has long been known as $C_5H_4N_4O_3$. As a rational formula, Medicus suggested the structure



and this has been proved by Emil Fischer[35] to be correct. The latter investigator was the one to show that uric acid is only one of a large series of allied substances known as the purin bodies, since they are all derivatives of a substance, which Fischer discovered and made synthetically, known as purin $C_5H_4N_4$. All these purin bodies contain

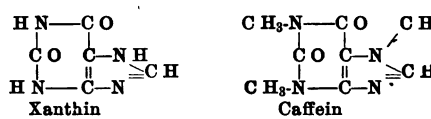
35. Fischer, E.: Synthesen in der Puringruppe, Ber. d. deutsch. Chem. Gesellsch., xxxii, 1899, 435.

the group C_5N_4, the atoms in this group (the so-called "purin nucleus") being arranged thus:



"Purin-nucleus." Purin.

Each atom of the purin nucleus is given a number as just indicated, and the various substances containing it are best designated according to this scheme. Thus if the structural formula for uric acid given above be examined, it will be seen that it consists of the purin nucleus with three oxygen atoms attached to it, one to the second atom, one to the sixth atom and one to the eighth atom of the nucleus; the chemical name for uric acid is, therefore, 2.6.8-trioxypurin. Similarly xanthin, which has the structural formula shown



Xanthin Caffein

is chemically called 2.6-dioxypurin. Caffein (contained in coffee) has the same formula as xanthin except that the hydrogen atoms attached to the first, third and seventh atoms of the purin nucleus in purin are replaced by methyl groups; caffein is accordingly designated as 1.3.7-trimethylxanthin. If one hydrogen atom of purin be replaced by the amido group, NH_2, we get adenin (6-aminopurin), or replace one H atom by NH_2 and add an oxygen atom and guanin (2-amino-6-oxypurin) results. Xanthin, hypoxanthin, adenin and guanin are all constituents of the cell nucleus and forerunners of uric acid. Caffein of tea and coffee, theobromin of

cocoa and theophyllin are all purin bodies, capable of transformation into uric acid.

Pure uric acid is a light white powder, seen microscopically to consist of rhombic tablets. It dissolves in water with extreme difficulty. At 18° C. the solubility in pure water is 1 to 39,480, that is to say, a liter of a saturated solution contains only 0.0253 gram of uric acid.

The physical chemistry of uric-acid solutions has been carefully studied by His and Paul.[36] The subject is complex and can not be gone into fully here; these recent studies, however, have thrown great light on the conditions of solubility of uric acid and the cause of its precipitation, and have knocked the bottom out of a whole series of erroneous theories of gout and the so-called uric-acid diathesis. It will be sufficient for the purposes of this review to epitomize the chief facts which have been established.

On dissolving in water, a part of the uric acid undergoes ionic dissociation into positive hydrogen ions and negative ions, just as HCl dissociates in aqueous solution into hydrogen ions (hydrion) and chlorin ions (chloridion). But, since uric acid has two hydrogen atoms that can be replaced by metals, that is to say, since it acts as a dibasic acid, it undergoes dissociation in two stages. The primary dissociation is into the hydrogen ion or hydrion ($H^{\cdot}$) and the univalent anion ($C_5H_3N_4O_3'$); in the secondary dissociation, a part of the univalent anion divides into a second hydrion ($H^{\cdot}$)

36. His, W., Jr.: Physikalisch-chemische Untersuchungen über das Verhalten der Harnsäure und ihrer Salze in Lösungen, Verhandl. des xviii Kongr. f. inn. Med., 1900, 425; also His, W., Jr., u. Paul, Ztschr. f. physiol. Chem., xxxi, 1900, p. 1.

and the bivalent anion ($C_5H_2N_4O_3''$). The primary dissociation is the greater one; the secondary is so slight as to be almost negligible. The more dilute the solution the greater the degree of dissociation; the more concentrated the solution the greater the number of undissociated molecules, so that in a saturated solution only about 10 per cent. of the molecules are dissociated. The number of undissociated molecules is proportional to the number of hydrogen ions in the solution, and if the latter be increased, for instance by the addition of a dilute mineral acid, the number of undissociated molecules of the uric acid becomes immediately augmented, and, since it is the undissociated acid which is extremely insoluble, a part of it will fall out of solution as a precipitate. This explains why the presence of other acids in solutions of uric acid decreases the solubility of the latter.

Corresponding to the two anions above mentioned, the univalent and the bivalent, uric acid yields with bases two series of salts, the so-called urates. Thus, if to a suspension of uric acid there be added a solution of sodium hydrate (NaOH), the uric acid will disappear and, instead, the primary urate of soda (acid urate, biurate, or, better named, mononatrium urate) will fall down as a precipitate; after the uric acid has all been changed in this way the primary urate in turn will be transformed by the further action of NaOH into the secondary urate (neutral urate, or, better, dinatrium urate), and this, being easily soluble, quickly dissolves. Now add any acid to this solution of dinatrium urate and uric acid will at once fall out of solution.

A study of mononatrium urate has shown that

it has the tendency to be precipitated in the form of transparent amorphous spheres and that, on standing, these spheres become gradually transformed into needle-shaped crystals; there is no change in chemical composition, simply an alteration of the physical form. The amorphous spheres yield with water certain opalescent (or even clear) false solutions—the so-called colloidal solutions; such colloidal solutions may contain an enormous quantity of urates, far more than can be dissolved in the same amount of water to make a genuine solution. On standing the colloidal solutions gradually give rise to saturated genuine solutions and the excess of urates present then falls out in the form of the crystalline salt.

The English investigator, Roberts,[37] has postulated the existence of a so-called quadriurate of soda, each molecule having the composition ($C_5H_3N_4O_3Na+C_5H_4N_4O_3$); if the substance really exists, it would be better called heminatrium urate, but there is no valid evidence that it does exist. As Tunicliffe and Rosenheim[38] have suggested, Roberts probably had to deal with variable mixtures of uric acid and mononatrium urate. As far as can be seen at present, we have to consider only two sodium salts of uric acid, mononatrium urate ($C_5H_3N_4O_3Na$) and dinatrium urate ($C_5H_2N_4O_3Na_2$).

The bearing of these chemical and physical studies of uric acid and the urates on the problems of the urinary excretion in health and in disease will be obvious as we proceed with this review.

37. Roberts, W.: On the Chemistry and Therapeutics of Uric Acid, Gravel and Gout (Croonian Lectures), London, 1892.

38. Tunicliffe, F. W., and Rosenheim, O.: Contribution to Our Knowledge of Uric Acid Salts, Lancet, lxxviii, 1900, p. 1708.

CHAPTER X.

THE URIC ACID AND URATES OF THE URINE AND OF THE BLOOD AND LYMPH.

Importance of a Knowledge of the Mode in Which Uric Acid Exists in the Urine and Blood—Formation of the Brick-Dust Deposit in Normal Urine on Standing—Conditions of Solubility of Uric Acid in Urine—Studies of Zerner and Ritter on Dinatrium Phosphate as a Solvent—Conditions of Solubility in Blood Less Well Understood—Ideas of Minkowski and Goto.

Having considered the general physical and chemical properties of uric acid, we are now prepared to review the opinions bearing on the form in which uric acid and the urates exist in the urine on the one hand, and in the tissue juices and the blood on the other. More than ordinary interest attaches to the conditions through which it is held in solution in the body, and a great deal of work has been done to determine the form in which it is precipitated in gouty deposits and in urinary sediments and concrements. Much study has been devoted to the factors which determine such precipitation and sedimentation.

In fresh, normal urine, the uric acid and urates are always in solution, but on standing a sediment tends to form. This may be either a red, sand-like crystalline powder which collects on the bottom or on the sides of the container, or it may take the form of the well-known reddish-gray brick-dust deposit, the so-called *sedimentum latericium*, which makes the urine uniformly turbid but easily clears up on heating. If the brick-dust deposit be permitted to stand for some time, red crystals gradu-

ally separate out, the latter do not redissolve on warming, and, microscopically, they are seen to be crystals of free uric acid. The brick-dust deposit itself is now known to consist of amorphous mononatrium urate, whereas the crystalline deposit on the bottom and sides of the container may consist of crystallized mononatrium urate alone or of the same substance mixed with crystals of uric acid.

It has been shown that the formation of the sediment, though partly due to cooling, is generally caused by a chemical transformation in the urine; as the precipitate falls out the acidity of the urine is diminished.[39] This chemical change consists in a reaction between the mononatrium urate and the mononatrium phosphate; neutral phosphate of soda and free uric acid are formed. The whole process can be imitated artificially, as Camerer has shown. This investigator mixed a saturated solution of mononatrium urate, which is alkaline to litmus, with a solution of mononatrium phosphate, which is acid to litmus; both fluids were kept at a temperature of 37° C. The reaction of the mixture was acid while it remained warm, but on cooling it turned alkaline and crystals of uric acid fell out of the solution. On warming the whole mass again, the uric acid redissolved and the alkalinity yielded to acidity.

The literature contains a vast number of researches dealing with the conditions of solubility of uric acid in the urine. Since uric acid is more soluble in an aqueous solution of urea than it is

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39. Voit, C., u. Hofmann: Ueber das Zustandekommen der Harnsäuresedimente, Sitzber. d. k. bayer. Akad. d. Wissensch., I, 1867, p. 279.

in water, Rüdel[40] maintained that in all probability a urate of urea is present in the urine. Roberts[41] believed that the uric acid excreted in the urine comes out of the kidneys as heminatrium urate (his quadriurate) and that this decomposes on standing into mononatrium urate and free uric acid. Pfeiffer[42] advanced the hypothesis that a double salt is formed between sodium urate and sodium phosphate and that the solubility in the urine is thus accounted for. These views of Rüdel, Roberts and Pfeiffer have not, however, stood the test of control experiments.

By far the best researches that deal with this phase of the subject are those of Zerner[43] and Ritter.[44] Zerner showed conclusively the dependence of the solubility of the uric acid and urates in the urine on their relations to the neutral phosphates present. It was he who first took up the systematic study of the influence of the phosphates on the solution of uric acid. All who have worked at the subject since have confirmed his main point, namely, that dinatrium phosphate is the most important solvent of the uric acid in the urine and possesses the power of hindering the decomposition

40. Rüdel, G.: Zur Kenntniss der Lösungsbedingungen der Harnsäure im Harne, Arch. f. exper. Pathol. u. Pharmakol., xxx, 1892, p. 469.

41. Roberts, W.: On the Chemistry and Therapeutics of Uric Acid, Gravel and Gout, Croonian Lectures, London, 1892.

42. Pfeiffer, E.: Ueber Harnsäureverbindungen beim Menschen, Berl. klin. Wochnschr., xxxi, 1894, p. 913.

43. Zerner, T. J.: Ueber die chemischen Bedingungen für die Bildung von Harnsäuresedimenten, Wiener klin. Wchnschr., vi, 1892, p. 272.

44. Ritter, A.; Ueber die Bedingungen für die Entstehung der Harnsäuresedimente; ein Beitrag zur Theorie der Gicht., Ztschr. f. Biol., xxxv, 1897, p. 155.

of urates into free uric acid. While the natural tendency of mononatrium phosphate in the urine is to act by decomposing urates into uric acid, this salt is ineffective as long as a sufficient amount of dinatrium phosphate is present along with it. Ritter's work has confirmed that of Zerner and has done much to clear away all the other vague or conflicting theories. Our knowledge of the conditions of solubility of uric acid and urates in the urine may be considered as tolerably satisfactory.

The matter of our knowledge regarding the conditions of solubility in the blood and the tissue juices is quite different. The old idea of v. Wittich[45] that uric acid exists in the blood as dinatrium urate and that it is deposited in the tissues in gout on account of a decomposition in the latter due to their high holding in carbonic acid, the dinatrium urate being transformed into the much less soluble mononatrium urate, was accepted by Pawlinoff[46] (1875) and by other investigators for a long time after, but is now regarded as highly improbable. Nor have the views of Roberts, that the uric acid in the blood is present as heminatrium urate, or of Pfeiffer, that it exists as a double salt formed by the union of mononatrium urate with dinatrium phosphate, any more in their favor than have the similar views regarding the conditions of solubility of the uric acid in the urine.

A gleam of new light came with the suggestion of Minkowski[47] that possibly uric acid circulates in

45. v. Wittich: Ueber Harnsekretion und Albuminurie, Virch. Arch., x, 1856, p. 325.

46. Pawlinoff: Die Bildungsstätte der Harnsäure im Organismus, Virch., Arch., lxii, 1875, p. 57.

47. Minkowski, O.: Ernährungstherapie bei harnsäurer Diathese, Gicht, Arthritis deformans, Oxalurie, und Phosphaturie, Leyden's Handbuch der Ernährungstherapie, ii, p. 499.

the blood, not in the form of a salt, but in loose union with some organic atom complex. He has shown experimentally that if an alkaline solution of chemically pure nucleinic acid be mixed with a solution of urate of soda, the addition of acetic acid no longer causes a precipitate of uric acid, nor can the uric acid be precipitated with the ordinary silver-magnesia mixture. Goto[48] in 1900 came to similar conclusions independently, and showed that thymin acid forms compounds with uric acid which behave entirely differently from ordinary uric acid or urates and which escape detection by our ordinary method of qualitative or quantitative estimation. It is not impossible, therefore, that the uric acid in the blood may be combined in some such way. If so, far greater amounts of it may be present in the blood and body juices than we have hitherto thought probable, for if it exists under some such conditions as those mentioned, it must have escaped detection.

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48. Goto, M.: Ueber die Lösung der Harnsäure durch Nukleinsäure, Ztschr. f. physiol. Chem., xxx, 1900, p. 473.

CHAPTER XI

URIC ACID IN DISEASE; ITS PATHOLOGIC PHYSIOLOGY.

Knowledge of the Pathology of Uric Acid Extremely Meager—Relation of the Substance to Gout and the So-called "Uric-Acid Diathesis"—Relation to Diseases Like Pneumonia and Leukemia—Uratic Nature of Gouty Deposits—Older Theories of Gout.

Up to the present time our review has dealt chiefly with the researches bearing on the normal physiologic relations of uric acid, and we have, we believe, presented to our readers, though in very brief form, most of the important facts which may be considered as established in connection therewith. We desire now to turn to a consideration of the studies made on uric acid in disease, in other words, to the pathologic physiology of the substance. Though the discussion of this side of our topic will doubtless be even more interesting to our readers than that of the normal physiology, it is necessary to confess in the beginning that only a small number of definite facts on the pathologic side have thus far been accumulated, and that our knowledge of the significance of uric acid in pathologic processes is extremely fragmentary. In the researches on the pathology of uric acid we find investigators indulging in assumptions and theories, as a rule, rather than reporting facts—the articles on the topic teem with "poetry," and are singularly deficient in content of recognizable "truth."

Of the various conditions in which deviations from the normal uric-acid relations have been observed, two stand out prominently from the rest,

inasmuch as in them it has become matter of common belief that the clinical manifestations are directly due to these deviations; we refer to gout and to the so-called uric-acid diathesis. In diseases like pneumonia and leukemia, in which, as we have seen, uric-acid formation and excretion may be increased, no one attributes the cause of the diseases or the symptoms of the patients to the altered uric-acid metabolism; it is assumed that the change in the uric-acid relations is, in them, a secondary phenomenon, a modification resulting from the primary pathologis process. Even in the uric-acid diathesis there is a good deal of evidence to indicate that we are concerned merely with altered conditions of solubility of uric acid and urates rather than with real disturbances in uric-acid formation and destruction; so that it is practically in gout alone that disturbances of actual uric-acid metabolism are held primarily responsible for abnormal clinical manifestations.

In gout, as everybody knows, two characteristic clinical phenomena are met with—the so-called gouty attacks of inflammation and the gouty deposits or tophi. The attacks of gouty inflammation are especially prone to affect the small, distal joints of the extremities, the metatarosophalangeal joint of the great toe being most frequently involved. The arthritis of gout is distinguished further from the other arthritides (1) by its frequent relation to excessive eating or drinking, (2) by its tendency to come on suddenly in the night, and (3) by the marked participation in the inflammatory process of the soft parts surrounding the joint. The gouty deposits or tophi, on the other hand, occur, usually without any accompanying acute

inflammatory reaction in their neighborhood. No matter, then, to what theory of gout we incline, we must see to it that our theory accounts for the origin of the acute gouty attacks of inflammation, that it explains how the tophi arise, and that it gives us some clue to the sites of predilection, both of the inflammations and of the gouty deposits.

Even before the end of the eighteenth century, shortly after the discovery of uric acid itself, Wollaston demonstrated the uratic nature of gouty deposits, and gave expression to the view that uric acid, in some way or another, stands in definite relation to the pathologic physiology of gout. Though Wollaston's idea received support from Forbes and later from Cruveilhier, it was strongly opposed by Scudamore, an authority whose opinion had great weight with his contemporaries. Accordingly, we find in the early part of the nineteenth century a whole series of hypotheses developed to explain the essential nature of gout, independently of the relation of uric acid to it. Some attributed the disease to alterations in the vascular system, others to intestinal disturbances, still others regarded it as of neural origin, and finally, there were those who believed it to be due to a toxemia, to the existence of some *materia morbi* circulating in the blood.

Scudamore himself asserted that gout is due to weakness of the blood vessels in the portal system, and that as a result there is abnormal secretion of the bile, and, indeed, a general disturbance of secretion throughout the intestinal canal. Gardiner held that the gouty pains are due to the rupture or extreme dilatation of capillaries around the fine nerve fibers as a result of venous congestion. Parry maintained that the essential pathology of gout

consists in an uneven distribution of the blood, and that the gouty paroxysm is to be viewed simply as an effort to restore the normal equilibrium. Of those who favored an intestinal origin, Sutton and Todd, both English physicians, may be mentioned. Todd's idea was that in gout, through some pathologic activity of the duodenum, there is increased formation of lactic acid, and further, that, owing to hepatic disturbances, biliary constituents are retained in the blood. Cullen was the special champion of the theory of a nervous origin of gout; the affection of the nervous system leads, he thought, to a depression of tonus. That gout is due to some sort of toxemia was the view advanced by Henry Holland, though he did not speculate as to the exact nature of the noxa concerned.

Note how gratuitous were most of the assumptions in these older theories of gout! For the most part, they were mere creations of the imagination, unsubstantial fumes of fancy, effects of the indulgence of revery. Such stretches of the imagination, uncontrolled by actual observation and scientific experiment, have never brought us far in medicine, and never can bring us far. Instead, Nature must be interrogated and she must be compelled to answer the questions herself. If we are to get accurate ideas regarding what goes on inside a gouty patient, we must draw the information in some way out of the patient himself, and take it into our minds through the medium of our organs of sense; we may not hope to attain to any significant truth in the matter simply by the use of our so-called "mind's eye." To some of the objective studies of gout in contrast with these subjective inventions it is our intention to advert in the next installation of this review.

CHAPTER XII.

THE EXCESS OF URIC ACID IN THE BLOOD IN GOUT.

Studies of Garrod—The "Thread Test"—Control of Garrod's Experiments—Accurate Estimations of Magnus-Levy by the Ludwig-Salkowski Method—Definite Proof Brought of an Excess of Uric Acid in the Blood in Gout—Similar Excess in Conditions Other than Gout—Doubt Regarding Relation of Uric-Acid Excess to Clinical Symptoms.

The suggestion of Wollaston[49] that in some way or another uric acid is definitely related to the pathology of gout followed, as we have seen, his demonstration of the uratic nature of gouty deposits. It received unexpectedly great support about the middle of the last century through certain observations of Garrod,[50] which led that physician to conclude that the blood of gouty patients contains an abnormally large amount of uric acid.

Garrod introduced what is known as the "thread test" for uric acid in the blood. To a little blood collected in a watchglass is added some dilute acetic acid; a linen thread is immersed in the mixture and the whole allowed to stand for twenty-four hours, evaporation being prevented. If the uric acid in the blood is increased, crystals of uric acid separate out, according to Garrod, adhere to the thread and can be recognized under the microscope. The results of the application of this thread test led Garrod to the belief that the quantity of

49. Wollaston: Gouty and Urinary Concretions. Phil. Tr., Lond., vol. ii, 1797, p. 386.

50. Garrod, A. F., Researches on Gout. Medicochir. Tr., vol. xxv, 1848, p. 83, vol. xxxvii, 1854, p. 49.

uric acid in the blood is always increased in gout, not only during the attacks, but before them and in the intervals between attacks. Indeed, his findings indicated that the increase is greatest shortly before an attack, and he ventured the opinion that this increase is directly responsible for the attack.

These remarkable observations of Garrod naturally excited great interest and a large number of control observations began to be made by various clinicians. Prominent among those who have confirmed Garrod's findings, almost in their entirety, may be mentioned Bence-Jones, Ranke, Charcot and more recently Sir Dyce Duckworth. The results of other investigators have been confirmatory of Garrod's work only in part; thus Salomon found an increase of uric acid in the blood in the acute attacks only, not before or after them, while Cantani supported Garrod as far as chronic gout is concerned, but agreed with Salomon as to the findings in acute gout.

A strong opponent of Garrod's view appeared in Emil Pfeiffer,[51] who urged that a positive finding with Garrod's test does not necessarily indicate an increase of uric acid in the blood, but rather that the blood at the time contains its uric acid in some form which dissolves with difficulty; in other words, that the substance exists in the blood as some "easily separable" modification. We know now from the chemical and physical studies of uric acid which have since been made that Pfeiffer's objection is not valid, for when uric acid separates out of solution this is almost always due not to

51. Pfeiffer, E.: Natur und Behandlung der Gicht. Verhandl. des vii, Kong. f. inn. Med., 1889, 166.

alterations in the chemical nature of the uric acid but to alterations in the conditions of solubility of the substance.

Obviously, to make Garrod's findings more conclusive, it was desirable that they should be controlled by exact quantitive estimations of the uric acid in the blood. Garrod and Salomon both attempted this, but unfortunately made their determinations with the inaccurate method of Heintz. Studies with more exact methods were made by Klemperer and later by Strauss, but the best research of all in this particular field is that of Magnus-Levy,[52] published in 1899. The latter made accurate determinations of the uric acid in the blood in no less than 17 cases by gravimetric analysis, using the reliable Ludwig-Salkowski method. His research has taught us that the uric acid of the blood is always increased in gout; there is, however, no constant increase just before an attack in contrast with the amount present in the free intervals such as Garrod thought he could demonstrate.

The most superficial and unreliable work recorded on the amount of uric acid in the blood in gout is, perhaps, that of Haig. Using a method which rests on a pure assumption and which has no well-founded chemical basis, he has drawn, as Luff and others have shown, wholly unwarrantable conclusions.

If we have good ground, and we think we have, for believing that the uric acid of the blood is increased in amount in gout, the question naturally

52. Magnus-Levy, A.: Ueber Gicht; klinische Beobachtungen, chemische Blutuntersuchungen. und Stoffwechselversuche. Ztschr. f. klin. Med., vol. xxxvi, 1899, p. 353.

arises, is such an increase pathogonomonic for gout or is it met with also in other conditions? The pathognomonicity of the symptom must be denied, for an increase of uric acid in the blood is found in nephritis (Garrod[53]) in diseases in which the red blood corpuscles are injured (v. Jaksch), and, temporarily, in health after nuclein-feeding (Weintraud). These facts have led many to think that perhaps after all the increase of the uric acid in the blood may not stand in any very definite relation to the main symptoms of gout. Some even go so far as to hold that the increase is to be regarded as merely accidental, a view recently supported with some vigor by Zagari.[54] Others, among them Cantani and von Noorden, suggest that the increase of uric acid in the blood is not the cause of gout, but is due rather to the partial solution and absorption into the blood of the gouty deposits. Still, right or wrong, the prevalent belief, we think, is that an increase of uric acid in the blood in gout is, in the main, responsible for the clinical symptoms. Those who hold to this view, however, admit that the increase alone does not suffice to explain gout, and they conceive of certain alterations in the blood or tissues, or of external injuries, as accessory etiologic factors.

In any case, we stand before the fact that the uric acid of the blood is increased in gout, and it must therefore be important to search for the cause of such increase. One might think *a priori* of an increased uric-acid formation, of diminished uric-

53. Confirmed by Kam and v. Jaksch.

54. Zagari, G.: Il bilancio organico di un gottoso durante e fuori l'accesso. Napoli, 1898; also Zagari, G. e D. Pace, La genesi dell' acido urico e la gotta. Napoli, 1897.

acid excretion, of lessened destruction in the body of uric acid once formed, or, finally, of a combination of these different factors. An epitomizing of the actual work which has been done in this connection will be our next task.

CHAPTER XIII.

THE EXCRETION OF URIC ACID IN GOUT: ITS RELATION TO THE EXCESS IN THE BLOOD.

Complications of the Problem—Ignorance Regarding Uric-Acid Destruction in Gout—Influence of Gouty Deposits on Excretion—Other Factors which May Influence Amount of Uric Acid Excreted—Early Studies of Excretion in Gout by Garrod—Pfeiffer's Calculations of No Value—Endogenous and Exogenous Purin Excretion—Excretion of Alloxuric Bodies in Gout Not Characteristic—Uric-Acid Excretion in Chronic Gout and Between Attacks of Acute Gout Goes on within Normal Limits—Acute Attacks of Gout Are Accompanied by Increased, Though Preceded by Diminished Excretion.

Let us turn to the work which has been done on uric acid excretion in gout and see whether or not it permits us to draw any safe conclusions regarding the excess of uric acid now known to exist in the blood in this disease. In studying the physiologic side of uric acid, we made considerable use, it may be recalled, of investigations of uric-acid excretion in health in order to gain ideas concerning the formation of uric acid in the normal body. We made the probably legitimate assumption that the amount of uric acid destroyed in the healthy body is a tolerably constant quantity, and, since the amount of uric acid excreted in health is the algebraic sum of the uric acid formed and the uric acid destroyed, we thought it justifiable to make important deductions regarding uric-acid formation from a study of the uric-acid excretion. This simple method, however, is unreliable when we come to a study of uric acid in disease.

In gout, for instance, we know really almost

nothing as yet regarding the function of uric-acid destruction; it may be undisturbed, but it is also possible that it is markedly altered; indeed, there are investigators who suggest that the main cause of uric-acid excess in the blood in gout may be an impairment of the normal process of destruction in the tissues. At the time when it was supposed that uric acid arises in the body as a result of the incomplete oxidation of proteids, it was common opinion that its increase was due to its imperfect destruction, that is, to a failure of the body to oxidize proteids completely to urea. Now that we know that the uric acid of the body arises chiefly from nucleins and not from proteids there is danger of our losing sight of faulty destruction as a possible factor in causing an increase in uric acid in the blood; as Wiener points out, until it is disproved, this possibility should be borne in mind. An attempt was made by Klemperer[55] to subject the matter to direct experimental test. He instituted a comparison between the power of the blood in gout to destroy uric acid and that of the blood in health, but we need not refer to his conclusions, for we have already learned that the blood in health has scarcely any power of destroying uric acid, that function belonging to certain organs rather than to the blood.

We believe that, thus far, no experiments with the organ from gouty cadavers to determine their power of destroying uric acid have been made; until these are forthcoming, the question must be left open. Uric acid has been fed to gouty patients

55. Klemperer, G.: Lösung und Zerstörung der Harnsäure im Blute Gesunder und Gichtkranker; ein Beitrag zur Bewertung der Gichtmittel. Therapie der Gegenwart, 1901, 344.

by Weintraud; he asserts that the uric-acid excretion is sometimes increased thereby more than it is in healthy individuals, but his findings were not constant. We must admit, therefore, for the present, that changes in uric-acid excretion in disease give no clue to whether it is the formation of the substance or its destruction which is disturbed.

Another factor which must influence uric-acid excretion in gout and further complicate its problems consists in the deposition at one time and the absorption at another of the masses of mononatrium urate of the gouty tophi. At times of deposition the excretion of uric acid would be diminished by the amount deposited; at times of resolution and absorption it would necessarily be increased.

On surveying the whole field, therefore, and taking into account various possibilities, it will be seen that in gout an increased excretion of uric acid might be due (1) to increased formation, (2) to decreased destruction, or (3) to the solution and washing out of gouty deposits; while a decreased excretion might be due either (1) to the deposition of mononatrium urate in the tissues, or (2) to a retention of uric acid in the blood or tissues owing to impairment of function of the excretory organs, the kidneys. When it is remembered that not one only of these factors but several of them together may be concerned in a given case, the complexity of the situation becomes obvious. No one ought to expect, in view of these considerations, that uric-acid excretion in gout will show any typical behavior, nor would any one, it would seem, be willing to draw any very far-reaching conclusions as to the pathogenesis of gout solely from a study of the

amounts of uric acid excreted, and yet we find in the literature numerous instances of attempts at deduction from such values!

Thus forewarned, we may safely give ourselves over to an examination of the results of researches which have dealt with the excretion of uric acid in gout. Most of them deal with excretion in the urine alone, the fees being unheeded, and none but the most recent have made any pretense to that completeness and rigor which we are coming to demand shall characterize serious studies in metabolism.

Garrod made the first determinations; he declared that a smaller amount of uric acid than normal is contained in the urine of chronic gout and also in that of acute gout in the intervals between attacks. Others, working on the subject between 1850 and 1880, confirmed Garrod's findings for chronic gout, and assumed that the diminished excretion is due to retention; the control experiments, however, could not support Garrod's ideas regarding acute gout for, though excretion in the intervals between attacks appeared occasionally to be diminished, examinations extended over a long period, though they showed considerable variations, yielded, on the average, normal values.

In 1889, Pfeiffer urged the necessity of establishing the physiologic limits of variability of uric-acid excretion; he himself attempted to do this, and concluded that the amount excreted in normal individuals per 100 kilograms of body weight is constant: Later, in 1892, he emphasized the importance of the relation of excretion of uric acid to that of urea and stated as his belief that when the proportion is greater than one of the former to

thirty of the latter, an abnormally high uric-acid excretion is going on. All these calculations of Pfeiffer lost their value, however, when it was shown that uric-acid excretion stands in no definite relation either to body weight or to the excretion of urea. We have seen that urea excretion is related to proteid metabolism, while uric-acid excretion is independent thereof, being chiefly a product of the decomposition of nucleins.

After Burian and Schur had demonstrated that the uric acid excreted consists of two compounds, an exogenous part dependent on the purins of the food and independent of the patient's individuality, and an endogenous part, individually different but constant for each individual, it became important in studying uric-acid excretion in gout to ascertain (1) whether the amount of endogenous purin is altered, and (2) whether feeding purins to the gouty patient affects the exogenous component as in health. The examinations made by Kaufmann and Mohr[56] in 1902 indicate that the values for both components are normal in gout. As yet no one has tested the power of the body in gout to form uric acid synthetically in comparison with that power in health; this should be done.

After 1880, a number of investigators opposed Garrod's ideas regarding diminished uric-acid excretion in gout. Bouchard, in 1885, declared that the excretion is not diminished between the attacks of acute gout, but instead is normal in amount or even increased, and Mordhorst's (1891) figures average distinctly above normal. Since then, Vogel in 1893, Klemperer in 1895, and Camerer

56. Kaufmann, M., u. Mohr, L.: Beiträge zur Alloxurkörperfrage und zur Aetiologie der Gicht. Deutsches Arch. f. klin. Med., lxxiv, 1902, 348, 586.

in 1896, have carefully studied uric-acid excretion in gout and obtained similar results. An analysis of all the data available affords no convincing evidence that gout, in the chronic stage or in the intervals between acute attacks, has any characteristic influence on the amount of uric acid excreted. Kolisch,[57] in 1895, believed that he could explain the contradictory results of his predecessors by a comparison of the amount of uric acid excreted with that of the alloxuric (xanthin or purin) bases. According to his view, uric acid is formed in the kidneys, from xanthin bases, and the amount of uric acid excreted depends on the functional condition of the kidneys. He asserted that the total alloxuric nitrogen is always increased in the urine in gout, but in the early stages the kidneys are able to convert the xanthin bases into uric acid and the uric acid in the urine is increased, while, in the latter stages, when the function of the kidneys is impaired, the xanthin bases are less completely converted into uric acid and are partly given off as such in the urine, the amount of uric acid excreted in the urine becoming normal or even diminished in amount. These findings excited much interest, but careful controls made by Weintraud in 1895, Rommel in 1896, Schmoll in 1896, and Badt in 1896, failed to confirm them, so that Laquer,[58] summing up the whole matter, was able to state positively that in gout the alloxuric bodies

57. Kolisch, R.: Ueber Wesen und Behandlung der uratischen Diathese, Stuttgart, 1895. See also Ueber Wesen und Behandlung der Gicht, Wien. klin. Wochnschr., viii, 1895, p. 787.

58. Laquer, B.: Ueber die Ausscheidungsverhältnisse der Alloxurkörper im Harn von Gesunden und Kranken. Verhandl. d. xiv Kongr. f. inn. Med., 1896, 353.

behave in no constant or characteristic fashion; the alloxuric bodies are not increased *in toto* in the urine, nor is the excretion of the bases increased over that of uric acid. During the decade just past, investigators in numbers have confirmed this statement. We may therefore regard it as well established that the excretion of uric acid and the purin bases in chronic gout, and in acute gout in the intervals between attacks, goes on within normal limits. Despite this restriction of the excretion to normal limits, there is one feature of the excretion, however, which is striking—there is a great variability in the purin excretion as contrasted with the constancy of the values in the same circumstances in health.

We must emphasize the fact that the relations dwelt on at some length above do not hold for the acute gouty attack. In it the uric-acid excretion is very typically altered. Views regarding the behavior in the acute attack were for a long time conflicting, but, thanks to the laborious researches of the younger His[59] and his colleagues, the matter has been definitely settled. The acute gouty attack is ushered in by a diminution in the amount of uric acid excreted, this diminution tending to precede the attack by two or three days. When the joint symptoms begin to appear, the amount of uric acid excreted increases and remains for some days considerably above the average level; then it gradually

59. His, Jr., W.: Untersuchungen an Gichtkranken. Wien. med. Blätter, xix, 1896, 291. See also Ueber Gicht, Schmidt's Jahrb., ccl, 1896, 266, and (with Cohnheim, Freudweiler, Respinger and H. His), Die Ausscheidung der Harnsäure im Urin der Gichtkranken mit besonderer Berücksichtigung der anfallsfreien Zeiten und bestimmer Behandlungsmethoden. Deutsch. Arch. f. klin. Med. lxv, 1900, 156.

sinks until the average level of excretion is regained. If several joints are involved, there is a corresponding depression of excretion preceding every new attack, followed by the typical increase. Only when the attacks follow each other very irregularly does the picture become confused. This behavior of the uric-acid output in acute gouty attacks has been confirmed in this country by Futcher of Johns Hopkins; in Germany, Magnus Levy's findings agree with those of His regarding the increased output in the attack, though they do not seem to indicate a premonitory diminution. Wiener,[60] in his admirable review, epitomizes the whole subject with the statement, "While, therefore, we dare not assume that in gout as a whole the excretion of uric acid behaves in any characteristic way, we may grant that there is constantly a greater excretion in the acute gouty attack than in the free intervals, even if the excretion does not exceed normal limits; probably the attack is preceded by a somewhat diminished excretion."

It seems likely that this behavior of the uric-acid excretion during the acute attack is due first to a retention and then to a "sweeping out" of the previously retained uric acid. If this be the case, the fact is for the highest interest in connection with the pathogenesis of the acute attack of gout, but it is of no help in explaining the constant increase of uric acid in the blood in gout. Indeed, the study of uric-acid excretion has thus far thrown no light on this dark point; it does not tell us whether the increase in the blood is due to diminished destruction, to increased formation, or to retention.

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60. Wiener, H.: Die Harusäure in ihrer Bedeutung für die Pathologie. Ergebn. d. Physiol., ii, Abt. 1, 1903, 377.

CHAPTER XIV.

THE TOTAL NITROGEN AND THE TOTAL PHOSPHORIC-ACID METABOLISM IN GOUT.

Irregular Alteration of Periods of Nitrogen Retention with Periods of Nitrogen Deficit in Gout—Theories Attempting to Explain Nitrogen Retention—The Phosphoric-Acid Balance—No Light Thrown on the Relation of Uric-Acid Excretions to Excess of Uric Acid in the Blood.

The failure of studies of uric-acid excretion in gout to throw light on the cause of the excess of uric acid in the blood has been made evident. It now becomes necessary to ascertain whether or not studies of the total nitrogen metabolism or researches on the total phosphoric-acid metabolism in gout give us any help in connection with the problem referred to.

Certain earlier studies on the excretion of urea in gout may be neglected since in the determination no attention was paid to the nitrogen intake; moreover, these earlier investigations yielded contradictory results, some of them indicating that the amount of urea excreted in gout is increased, others that it is diminished.

The researches of Schmoll,[61] in 1896, since confirmed by Magnus-Levy, Zagari and others; were among the first that attained to that degree of completeness which makes such studies valuable. Vogel had shown that the excretion of urea is often abnormally low in gout, but Schmoll brought the proof that, at certain periods, the gouty patient excretes less nitrogen, then he ingests; in other words

61. Schmoll, E.: Stoffwechselversuche an einem Gichtkranken Ztschr. f. klin. Med., vol. xxix, 1896, 510.

that actual nitrogen retention occurs for a time. This retention is not permanent, however; later comes a period when the nitrogen excreted exceeds in amount the nitrogen ingested, when there is an actual nitrogen deficit. These periods of nitrogen retention and of nitrogen deficit alternate irregularly with each other.

The question at once arose, to what can these disturbances in nitrogenous metabolism be referred? The somewhat similar disturbances which occur in nephritis were thought of, but the explanations given for the conditions in that disease can scarcely hold in gout; in the latter, the urine does not necessarily contain albumin; and, further, the excretion of phosphoric acid, the first to be affected in nephritis, is not markedly altered. Magnus-Levy, however, advanced the view that, in the periods in gout when the total nitrogen excreted is increased, there is actual increased destruction of proteid, probably toxogenic, inside the body. In the periods of nitrogen retention he sees simply a convalescence from the former disturbance, times when the proteid destroyed is being rebuilt. Unfortunately for this view, the body weight during periods of nitrogen retention does not increase as much as it should if proteid is formed from the nitrogen retained; indeed, the body weight may actually decrease during nitrogen retention. Many, with Zagari, will be inclined to regard the form in which the nitrogen is retained as an open question, assuming only that the organism is in some way or another trying to replace a nitrogen loss of the details of which we are also ignorant.

Certain other attempts to explain the nitrogen retention must be referred to. Schmoll rejected

the hypothesis that it is due to uric-acid retention on the ground that the amount of nitrogen retained is far too great to be thus accounted for, and Hager's supposition that the nitrogen is retained, not as uric acid, but as adenin, may be similarly disposed of. An admirable metabolic research was made by Vogt[62] in 1901. He showed that the nitrogen retention is not explicable by an increase in proteid, for while the retention in one instance amounted to as much as 24.6 grams of nitrogen, the patient remained in phosphoric-acid equilibrium. Nor is it referable to the retention of total nuclein, for when nuclein was fed to his patient its phosphoric-acid content was promptly excreted, while the nitrogen excretion remained further than ever behind the nitrogen intake. He concluded, therefore, that the retention is at least partly due to purin nitrogen, the nucleins absorbed being split at once into phosphoric acid and purins, the excretion of the latter being delayed, thus indicating a high degree of sluggishness of purin metabolism in gout. Vogt admitted, however, that there are probably still other reasons for the nitrogen retention.

The most careful investigation of the phosphoric acid metabolism in gout we owe to Kaufmann and Mohr[63] (1902), who first thoroughly examined the "phosphoric-acid" balance." They undertook their studies in the hope that the results would help them to decide whether the loss of nitrogen at certain periods in gout is due to the breaking down of

62. Vogt, H.: Ein Stoffwechselversuch bei akuter Gicht. Deutsche Arch. f. klin. Med., vol. lxxi, 1901, 21.

63. Kaufmann, M., u. Mohr, L.: Beiträge zur Alloxurkörperfrage und zur Aetiologie der Gicht. 3 Teil, Stoffwechselbeobachtungen bei 5 Gichtkranken. Deutsches Arch f. klin. Med., vol. lxxiv, 1902, 586.

proteid or to the sweeping out of the "slag," and whether the nitrogen retention at other periods indicates an increase of proteid or merely a retention of end-products. They have concluded that no single explanation of retention or deficit of nitrogen is valid; on the contrary, nearly all contradictions vanish, they think, if we assume that entirely different processes, increase and destruction of proteid on one side, retention and "sweeping out" on the other, may be going on in a variable manner in different individuals and in different phases of gout.

Having thus shown that the nitrogen-excretion alone is not a safe criterion for judging of the causes of the alteration in uric-acid excretion, they turned to the phosphoric-acid excretion. In 1901, Loewi had suggested that the behavior of the latter in gout indicates that uric acid is retained in the disease; in health, on a constant diet, he found a constant relation between uric-acid excretion and phosphoric-acid excretion, while in gout the quotient deviated from normal and indicated uric-acid retention. Kaufmann and Mohr, however, find the quotient to be within normal limits, and, further, call attention to the fact that phosphoric-acid excretion varies with the varying needs of the body for phosphoric acid. Accordingly, it is unsafe to use the phosphoric-acid excretion or its relation to uric-acid excretion as evidence for the view that the causes of the excess of uric acid in the blood in gout is uric-acid retention.

CHAPTER XV.

OTHER FACTORS POSSIBLY CONCERNED IN OCCASIONING THE EXCESS OF URIC ACID IN THE BLOOD IN GOUT.

Retention Due to Diseased Kidneys—Arguments for and Against this View—Hypothesis of the Existence of Non-excretable Forms of Uric Acid—Hypotheses of Increased Formation of Uric Acid—Conclusions Regarding Cause of Excess in Blood in Gout.

Despite the discouraging results of the attempts to explain the excess of uric acid in the blood in gout by studies of uric-acid excretion, total nitrogen excretion, and phosphoric-acid excretion, investigators have tried in various other ways to get clues to the explanation of the phenomenon. Some have sought to show that the excretion of uric acid is faulty owing to disease of the kidneys, others that there is a retention owing to the occurrence in the blood either of a form of uric acid unsuitable for excretion or of conditions which are unfavorable to solution of ordinary uric acid and urates, and still others that there is an increased production of uric acid, oxidative or synthetic, owing to the hyper-activity of certain organs. No efforts have been made so far as we know to determine whether or not the destruction of uric acid which normally goes on in the body is decreased, though it is important that we should be definitely informed on this point.

The idea that uric acid is retained in the blood in gout on account of impairment of the excretory power of the kidneys, due to organic or functional disease, has been strongly held by Garrod, by Levi-

son, by Luff[64] and by Strauss,[65] and as strongly opposed by Cantani, by Ebstein, by Pfeiffer, by Schreiber,[66] by Schmoll, by Smith-Jerome and by Reach. Those who favor the view urge (1) that there are periods of diminished uric-acid excretion in gout, followed by periods of increased excretion; (2) that it is rare to find cases of gouty arthritis at autopsy unassociated with disease of the kidneys; (3) that it is common at autopsies on nephritic patients to find joint deposits which have been wholly unsuspected during life, especially in one particular form of kidney disease, namely, granular atrophy; (4) that toxic influences such as lead poisoning and alcoholism stand in an etiologic relation both to gout and to contracted kidney; (5) that uric-acid retention obviously occurs in nephritis and is associated with excess of uric acid in the blood; (6) that in gouty cases, without albuminuria or casts in the urine, defective functioning of the kidney may often be detected by observing beginning hypertrophy of the heart, changes in the eye grounds, nitrogen retention without increase in body weight, slowed excretion of methylene blue and alterations in the molecular concentration of the urine. On the other hand, those who oppose the view maintain (1) that the excess of uric acid in the blood in gout precedes the development of kidney disease and that many gouty patients have normal kidneys; (2) that the

64. Luff, A. P.: The Pathology and Treatment of Gout. Brit. Med. Jour., Lond., 1898, i, 150; 1066.

65. Strauss, H.: Pathogenese und Therapie der Gicht im Lichte der neuren Forschungen. Würzberger Abhandl., 1902, ii, 209.

66. Schreiber, E.: Gicht: Ueber die Harnsäure unter physiologischen und pathologischen Bedingungen. Stuttgart, 1899.

disease of the kidneys common in the later stages of gout is not the cause but the effect of the gouty disorder, and (3) that the kidneys in gout are capable of excreting far larger amounts of uric acid than normal if the formation of the substance in the body be markedly increased by thymus feeding. The first objection has been met in Minkowski's assumption that when the kidneys seem normal, in reality a functional disease exists in which the secreting elements of the kidney alone are affected, leading to an increase of the "threshold" for uric-acid excretion; and Strauss has tried to deprive the third objection of its force by bringing the proof that, even in true nephritis, uric-acid excretion may be increased by feeding large amounts of meat extract.

The hypothesis that an excess of uric acid accumulates in the blood in gout, not on account of diseased excretory organs, but owing to its existtence in some forms other than the ordinary—in a form, in fact, in which the kidneys can not seize hold of it to excrete it, is an old one; it was suggested as early as 1860 by Parkes, and has since been revived by various physicians. For a time Pfeiffer held this view, but the evidence he brought in favor of it by means of his so-called "uric-acid filter," has shown it to be invalid. Still, Minkowski has recently expressed the opinion that uric acid may circulate in the blood in a form which does not appear to be suitable for excretion into the urine, and the possible existence of such conditions should therefore be borne in mind. Others think it less probable that a special form of uric acid exists in the blood than that the conditions of solubility vary; a decreased

alkalinity of the blood, for example, being held guilty, by Roberts and others, for uric-acid retention.

In contrast with the above views, in which uric-acid retention is held answerable for the excess of uric acid in the blood in gout, are the speculations which assume that the established excess is the consequence of increased formation of the substance. When such speculations first arose, disease of certain organs—the spleen or the liver, according to the prevailing view at the time of uric-acid formation—was postulated as the cause of the increased production. At the period when uric acid was supposed to be derived from proteid by faulty oxidation, slowing of the metabolic process in various tissues, it was thought, could account for increased formation in gout and, later, when the oxidative origin from nucleins had been demonstrated, the excess of uric acid in the blood was attributed by some to hyperactivity of the bone marrow and muscles, by others to increased destruction of leucocytes and by still others to a generally increased cell destruction in the body. There is no proof, however, of the existence in gout of any of the conditions mentioned and, should they exist, it is not easy to see why their effects should not be neutralized either by increased destruction of uric acid or increased excretion of the same.

The question of an increase of uric acid by synthesis in gout has scarcely yet been put. Wiener suggests it as a possibility, on account of the relation of oxaluria to gout, but no experimental work of any importance in this connection has yet been done.

Finally, since we are totally ignorant of any

modification of uric-acid destruction in gout, we can sum up our knowledge concerning the cause of uric-acid excess in the blood by saying that it is not yet wholly clear, but that probably several factors are variably concerned, and that none of the factors alone can explain a permanent excess without the assumption of a pathologic retention, for otherwise equilibrium would always be restored by increased excretion.

CHAPTER XVI.

THE RELATION OF URIC ACID (OR URATES) TO GOUTY DEPOSITS AND THE ACUTE GOUTY PAROXYSMS.

Chemical and Histologic Studies of Tophi—Experimental Production of Tophi—Disputes as to the Nature of the Acute Gouty Attack — Studies of the Younger His — Hypotheses as to the Mode of Formation of Gouty Deposits—Not Due to Variations in Alkalinity—Influence of the Presence of Other Salts—Necessity of Assuming Localized Influences.

Many attempts have been made to explain the two chief symptoms of gout, the occurrence of gouty deposits or tophi, on the one hand, and the origin of the acute gouty inflammation or paroxysm on the other.

The tophi, which usually develop slowly and painlessly in the skin or in fibrocartilage, consist chemically chiefly of mononatrium urate with some admixture of monocalcium urate (Ebstein and Sprague[67]). The anatomy of the nodule has been carefully studied (Riehl,[68] Freudweiler[69]). Along with the uratic deposit in the center there is necrosis; this is surrounded by a connective-tissue capsule in which "foreign-body" giant-cells may occur; accumulations of lymphoid cells are met

67. Ebstein, W. u. Sprague, C.: Beitrag zur Analyse gichtischer Tophi. Virchows Arch., 1891, cxxv, 207.

68. Riehl, G.: Zur Anatomie der Gicht, Wien. klin. Wchnschr., 1897, x, 761. See also Ueber die Anatomie der Gichtknoten, Schmidt's Jahrbücher. 1897, cclliii, 271.

69. Freudweiler, M.: Experimentelle Untersuchungen über das Wesen der Gichtknoten, Deut. Arch. f. klin. Med., 1898, lxii, 266, and Experimentelle Untersuchungen über die Entstehung der Gichtknoten, ibid., 1901, lxviii, 155.

with about the adjoining vessels; doubly refractive granules may be seen inside the giant cells; a few crystals are present in the uninjured tissue at the periphery of the nodule. Precisely similar nodules can be produced experimentally by injection of mononatrium urate (Freudweiler), especially if alcohol be given at the same time (His, Jr.[70]). The nodule is not due to the mechanical action of the urate alone, but the urate, in addition, has a specific effect. The immediate cause of the deposit has not yet been made out, though hypotheses are rife regarding it.

The acute gouty inflammation has been ascribed by many to deposits of uric acid in the joint, but others assert that the acute attack may occur in the absence of deposits in or about the joint, and among these is Ebstein, who holds that the acute attack is due to stasis of urates in solution. Virchow pointed out that when deposits occur in the joints they are in the cartilage, while the inflammation involves the synovial membrane, not the cartilage. Some even deny that the joint is mainly involved, placing the irritative process in the skin (Pfeiffer, Aronsohn), in the lymph vessels (Mordhorst) or even in the peripheral nerves (Wade, Ewart). The inconstancy of the deposits is the point which is disturbing to the acceptance of the view that the acute attack is due to them, but it should be borne in mind that when they are not found they may really have been present for a time and subsequently may have been removed by solu-

70. His, Jr., W.: Nachtrag zu der Arbeit von Freudweiler, Deut. Arch. f. klin. Med., 1899, lxv, 618. Schicksale und Wirkungen des sauren harnsäuren Natrons in Bauch und Gelenkhöhle des Kaninchens. Deutsches Arch. f. klin. Med., 1900, lxvii, 81.

tion or by the activity of phagocytes. The studies by His, Jr., of uric-acid excretion in the acute attack have shown that uric acid is retained in the period just preceding the attack and is excreted in excess during the attack, a fact which makes it probable that deposits occur somewhere just before the attack and are redissolved again during the attack. But whether this fact stands in a causative relation to the attack, or is a mere coincidence therewith, is not known. Since deposits of urates are frequently found in the joint cartilages after an acute attack, and since in the attack it is the skin and soft parts about the joint (and not elsewhere) which are involved, it seems fair to localize the acute attack in the joint and its immediate neighborhood. Whether the deposits or their solution cause it, or simply accompany it, is not known.

Why the tophi should be painless and chronic and the paroxysm painful and acute has exercised the minds of various observers. It has been suggested that tophi occur in looser tissues, the deposits in firm cartilage leading to a more energetic inflammatory reaction (Garrod). It may be that the rapidity of the deposits is a factor, the tophi forming too slowly to be markedly irritative (Laquer), or it may be that the amount of the deposits dissolved determines the intensity of the inflammation, the deposit itself acting chiefly mechanically, while the dissolved urates act as chemical irritants; the motion at a joint might lead to rapid solution, with production of an acute attack (His, Jr.).

We have hinted that hypotheses concerning the mode of formation of the deposits are abundant. Some ascribe the precipitation to the excessive pro-

duction of uric acid in the blood and tissue juice; others to a decrease in the solvent power of the blood and juices for uric acid in some less soluble modification than the form we know; and still others to local changes in the tissues themselves rather than in the body fluids or in the uric acid or urates.

The hypothesis that the deposits are due to increased formation of uric acid in the blood has had but few supporters, but a large number of investigators have been appealed to by the view that the urates are precipitated on account of some diminution of the solvent power of the blood and juices. Many felt sure that the alkalinity of the blood is altered in gout, and there are a host of researches dealing with this point, most of them unfortunately with imperfect technic. The most reliable studies on the alkalinity appear to be those of Magnus-Levy[71]; from them it seems clear that, though the alkalinity of the blood is somewhat variable in gout, the variations occur within narrower limits than those which hold for normal individuals, and, moreover, variations are independent of the acute attacks. It is hard to see, anyway, why, if the deposits are due to diminished alkalinity of the blood, they should not be general instead of local. Ebstein, to avoid this difficulty, assumed locally limited acid production in the tissues as the cause of the deposits. He based his theory, however, on the ground that necrosis precedes the deposit, and this basis has been destroyed by the researches of His and Freudweiler, which

71. Magnus-Levy, A.: Harnsäuregehalt und Alkalescenz des Blutes in der Gicht. Verhandl. d. xvi Kongr. f. inn. Med., 1898, 266.

demonstrate, we think conclusively, that the deposits precede the necrosis. A better founded view than that of diminished alkalinity is one which supposes that the solvent power of the fluids is diminished through the presence of other salts in solution. The work of Roberts, Ritter and Strauss has gone far to show that deposition may depend on the relative amounts of other salts present, especially the amounts of mononatrium and dinatrium phosphate. Here, again, however, the question has to be asked, How can local rather than general precipitation be accounted for? Of the efforts to answer it none can be regarded as wholly satisfactory. Freudweiler thinks inflammatory change a prerequisite; von Noorden assumes the local activity of some ferment; Zagari and Pace suggest some local alteration in the vital activities of cell nuclei—all vague and unsupported hypotheses. That some local cause, however, must be conceived of as responsible for the local deposits seems necessary; we must wait for future researches to reveal it to us.

That distally placed joints and certain special fibrocartilages should be picked out by gouty deposits is certainly interesting and peculiar. It can be no accident that these particular localities are sites of predilection. Some believe that nervous influences are answerable—a disease of peripheral trophic nerves (Paget) or disturbances of trophic centers (Duckworth, Luff). Others point out that the parts affected are, as a rule, poorly vascularized. Some of the localities, such as the joint of the great toe, are unusually exposed to pressure and trauma. Possibly the fact that cartilages are rich in sodium salts (Roberts) may be a factor. That

the ears and peripheral joints, more than other parts, are exposed to cold is adduced by Mordhorst as, perhaps, important. Our knowledge at present is obviously wholly unsatisfactory regarding the matter.

To sum up this portion of our review, it may be said, then, that while the tophi and the acute gouty paroxysm appear in different ways, both are apparently associated with deposits of mononatrium urate. The mechanism of deposition is not yet wholly clear, though local conditions in the tissues must probably be held responsible in connection with the excess of uric acid in the blood. As to what those local conditions may be, we are as yet profoundly ignorant.

CHAPTER XVII.

THERAPEUTIC MEASURES DIRECTED TOWARD INFLUENCING URIC ACID FORMATION, DESTRUCTION AND EXCRETION. THE TREATMENT OF GOUT.

Recapitulation of Facts Established Regarding Uric Acid in Physiology and Pathology—Rational Treatment of Gout—Protection from Influences Known to Favor the Development of Gout—Efforts to Lessen Amount of Uric Acid Formed—Attempts to Increase Uric-Acid Excretion and Uric-Acid Destruction—Efforts to Increase Solubility in Blood and Tissue Juices—Absurdity of Many Vaunted Remedies—Empirical Treatment—Paramount Importance of Well-regulated Regimen—Local Applications.

We have reviewed in considerable detail, as we promised to do, the important work that has been done on this subject. The processes of uric-acid formation, excretion, destruction, retention, deposition and solution in health and disease have, one by one, been considered, and we have sifted as carefully as possible what we consider the wheat from the chaff. In a subject so complex it would be surprising if we did not include some worthless matter among the wheat and discard as refuse at least a little valuable grain. Despite the immense amount of work which has been done, it is surprising what a small bulk of well-determined fact has been accumulated and how much time and trouble have been required to prove the unreliability and harmfulness of a majority of the speculative views which have been advanced. Though the bulk of facts is not large, their value is precious, and we will do well to hoard them jealously and to rejoice that we may consider them by themselves, uncontami-

nated by the paltry rubbish in which they have been hidden.

It is worth much to us on the physiologic side to have grown familiar with the chemical and physical qualities and relationships of uric acid; to have realized its connection with nuclein metabolism; to have become acquainted with the distinction between exogenous and endogenous uric acid of oxidative origin, and between these and the uric acid of synthetic source; to have been informed, even partially, as to the way in which uric acid is destroyed in the body; to have determined, more or less accurately, the localization of the processes of uric-acid formation and uric-acid destruction; and to have recognized that the substance probably circulates in the blood chiefly as mononatrium urate or in combination with an organic substance. On the pathologic side it is important to us to have found out in what conditions deviations from the normal uric-acid relations have been observed and to have discovered that gout is the only disease in which there is yet any strong probability that disturbances of uric-acid metabolism are directly and mainly responsible for the clinical symptoms. It has been shown that uric acid is increased in the blood in gout; that the deposits in the joints and in the tophi in gout consist of crystalline mononatrium urate; that the former is dependent in all probability on irregularities in uric-acid excretion, including a slight diminution of the amount excreted before an attack and an increase later; that the local deposits at sites of predilection are in some way dependent on unknown local influences; that the acute gouty paroxysm is very prone to occur in the night; that the anomaly of metabolism respons-

ible for gout is often met with in a succession of generations in the same family; that the development of gouty symptoms in the predisposed may be favored by excessive eating, lack of exercise, abuse of alcohol, chronic lead poisoning, and digestive disturbances of various kinds.

The rational treatment of gout will, then, consist, first, in combating the primary disturbance of metabolism; the patient must be protected from all the influences which experience has taught us favor the development of gout. In addition, the effort may be made to prevent the accumulation in excess, or the deposition, of uric acid or urates in the body. This may be attempted in various ways: (1) by lessening the amount of uric acid formed in the organism, (2) by trying to increase uric-acid excretion. (3) by increasing uric-acid destruction, and (4) by making the effort to increase the solubility of uric acid in the blood and tissue juices.

The formation of exogenous uric acid is largely within our power: the amount can be diminished by limiting the forestages of uric acid—nucleins and purin derivatives—in the food. Hence in gout the eating of sweet-breads, liver and kidneys—all rich in nucleins—should be prohibited, and the amount of meat and meat soups permitted should be small. Peas and beans are also rich in purin bodies and should be sparingly allowed. The well-known harmfulness of beer in gout has been attributed by some to its relatively high purin content. The temporary relief afforded by purgatives may be due, in part, to the sweeping out of the forestages of uric acid from the intestine before they are absorbed. There is no certain proof that drugs can diminish uric-acid formation, though Weiss

has ascribed such an action to china acid. A large number of the much-vaunted "gout specifics" consist of this china acid combined with other drugs, e. g., urosin (china acid with lithium), sidonal (china acid with piperacin), chinotropin (china acid with urotropin), urol (china acid with urea) and "new sidonal" (china acid anhydrid). If china acid affects the symptoms favorably at all, we do not know how it does so; it has been suggested that, being tetraoxybenzoic acid, it is more or less allied to salicylic acid (monoöxybenzoic acid) and so may, like the latter, exercise a pain-stilling effect.

To increase uric-acid excretion the best means we have is to increase the secretion of urine, and that is best effected by copious water drinking; mineral water or any pure table water will do. Whether or not it is possible directly to increase uric-acid excretion by drugs is still disputed. It is thought by some that the salicylates (salicylic acid, salol, aspirin—monacetic-acidester of salicylic acid —etc.) increase the excretion of uric acid; others believe that they increase uric-acid formation, and still others think that the amelioration of symptoms caused by them in gout is due only to their pain-relieving and diaphoretic actions. Ideas as to their effect are chiefly preconceived; they have not yet been subjected to adequate experimental control.

Attempts to increase uric-acid destruction in the body have frequently been made, but there is no proof that there is any general diminution of the oxidative processes in gout, nor is there any basis for the view that drugs hasten uric-acid destruction, though alkalies, oxygen inhalations, thyreoid

tablets and spermin have all been recommended for the purpose!

The hypothesis which has appealed most to the profession and to the laity, and the one which, on the whole, has proved most profitable to the drug manufacturers, is that which attempts to prevent uric-acid deposits and gouty conditions by trying to increase the solubility of uric acid in the blood and tissue juices. Alkalies and especially bases which form very soluble salts with uric acid have been suggested for this purpose. The attempts are futile for two reasons. In the first place it has not yet been found possible, owing to the complexity of the blood and the tissue juices, to produce in them exactly the form of urate, the solubility-conditions of which are the most favorable. In the second place, the studies of His and Paul, applying the modern conceptions of physical chemistry, have shown that the solubility of any urate in the blood is decreased by the sodium salts of the blood. It does no good to bring into the solution along with mononatrium urate other bases whose uric-acid salts are more soluble than sodium urate; for physical chemistry has shown that on bringing an acid together with several bases the first salt to fall out is that whose "solubility product" is smallest. This fact holds not only for inorganic bases, like lithium, but also for organic nitrogenous bases, like piperacin (di-ethylen-diamin) and lysidin (ethylen-ethenyl-diamin), from which so much was expected. The whole group, therefore, of so-called "antilithics" and "uric-acid solvents" based on the above theory is robbed of any scientific support. If uric acid is to be rendered more soluble in the blood, it must be, therefore, by the formation of

some easily soluble combination with other organic atom-complexes, with production of substances which are not dissociable, i. e., are not "salts." Uric-acid and thymin acid (the phosphorous-containing residue of nucleinic acid) may combine in this way; the use of thymin acid (nucleotin-phosphoric acid) has been recommended in gout, but the pure substance is not yet commercially available for the purpose; the preparations on the market said to be pure contain in reality quantities of purin bases, and the increased excretion of uric acid following their administration may be due to the uric acid made by the body from the impure chemical itself. Indeed, some investigators doubt the existence of the substance called thymin-acid. Another substance with which uric acid forms a non-saltlike compound is formaldehyd, and it has been shown that on giving hexamethylene tetramin[72] the formahldehyd split off from it in the body appears in the urine as easily soluble diformaldehyd-uric acid. Another combination called citarin (formaldehyd combined with citric acid) is said to act similarly. It is as yet doubtful whether such substances ever exert any beneficial effect in gout. In addition to the preparations named many others are on the market, some of them of known composition, others advertised with vague statements regarding their content.

On the whole, the best that can be hoped from drugs at present in gout appears to be the relief of pain by the various antineuralgic substances, such as the salicylic preparations, with which every one is now familiar. One drug deserves special

72. This substance is on the market under the names urotropin, cystogen, aminoform, formin, etc.

mention here, and that is colchicum. It has an enviable empirical reputation. It can be used as tincture or wine or as pure colchicin, the latter given in pill form, 1/100 grain (.001 gram) in each pill. In acute attacks one pill may be given every half-hour or hour until three or four have been taken.

The best treatment of gout—the mainstay of therapy in the disease—consists in a well-regulated regimen. The diet must be carefully chosen and rather spare, as a rule. It should consist of 100 to 120 grams proteid, 80 to 100 grams fat and 250 to 300 grams carbo-hydrates (Minkowski). The amount of animal food should be moderate. that of easily digestible vegetable food more liberal. Pastry, confections, sharp sauces, mayonnaise, mushrooms and all foods hard to digest are to be proscribed. Alcohol and coffee should be forbidden or used in minimal amounts. Very weak tea may be permitted, but waters (especially slightly alkaline mineral waters) form the best drink. Two hours or more of gentle exercise in the open air daily, where not contraindicated, should be enjoined. In acute attacks rest and local applications are necessary. For the tophi or chronic residues in the joints local phagocytic activity may be excited by means of hot applications and massage. Two or three months of camping, with much rowing, sailing, canoeing and fishing often proves highly beneficial to gouty patients, provided the appetite is kept within control. Many a gouty individual has gotten a new lease of life by spending a summer judiciously in the Adirondacks or Rocky Mountains, on the coast of Maine, in the Wiscon-

sin or Michigan woods or among the 30,000 islands of the Georgian Bay.

After all, it may turn out that disturbances of metabolism, of a nature unguessed as yet by us, may be more important in the pathogenesis of gout than the disturbances of uric-acid metabolism discussed in this review.

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